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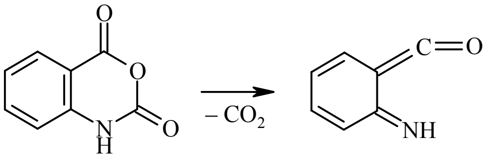
SYNTHESIS OF HETEROCYCLIC COMPOUNDS BASED ON ISATOIC ANHYDRIDES (2H-3,1-BENZOXAZINE-2,4-DIONES). (REVIEW)

M.-G. A. Shvekhgeimer

Data published after 1979 on the chemical transformations of 2H-3,1-benzoxazine-2,4-diones (isatoic anhydrides), leading to the formation of other heterocyclic compounds, are reviewed, classified, and analyzed.

Keywords: benzodiazepines, isatoic anhydrides, indoles, 1,3,4-oxadiazoles, 1,2,3-triazines, 1,2,4-triazoles, quinazoline-2,4-diones, quinazolones, quinolones

The wide range of chemical transformations characteristic of isatoic anhydrides is due largely to their ability to eliminate a CO_2 molecule with the formation of highly reactive imino ketones, as illustrated below for the case of the unsubstituted anhydride **1**.



1

There are at present two reviews, published before 1980 [1, 2], in which published data on the synthesis and transformations of isatoic anhydrides are discussed in detail.

The present review contains data on the synthesis of various nitrogen-containing heterocyclic systems based on isatoic anhydrides that have appeared in the press since 1980. It covers both the direct transformations of these anhydrides into such systems and processes leading at the first stage to the formation of anthranilic acid derivatives that are then transformed into the heterocyclic compounds in one or several stages. It is important that such transformations result in the formation of new heterocyclic systems.

Part 1 of this review gives a few examples of the transformations of isatoic anhydrides leading to the formation of products containing a five-membered heterocycle. In the second part the very large amount of data on reactions leading to systems containing a six-membered heterocycle is divided into several subsections. Processes leading to heterocyclic compounds with one, two, or three nitrogen atoms, with two different heteroatoms (N and O, N and S), and with two nitrogen atoms and a sulfur or phosphorus atom in the ring are discussed in this part. Part 3 contains a review of published data on the synthesis of benzodiazepine derivatives based on isatoic anhydrides. The transformations of these anhydrides into polycyclic systems containing at least two new condensed rings, each containing one or more nonbridgehead nitrogen heteroatoms, and also into macrocyclic compounds with nitrogen and oxygen atoms in the macrocycle are discussed in part 4.

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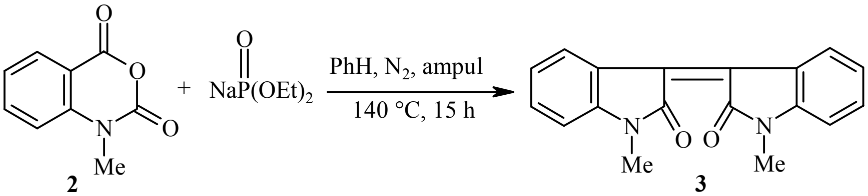
1. REACTIONS LEADING TO THE FORMATION OF FIVE-MEMBERED HETEROCYCLES

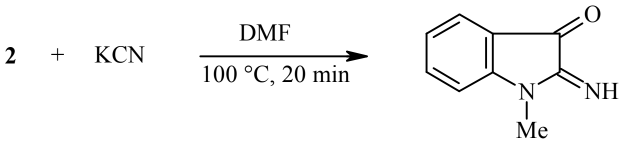
As already mentioned, there are few papers on the transformations of isatoic anhydrides into compounds containing a new five-membered ring.

N,N[1]-Dimethylisoindigo (**3**) was synthesized with a yield of 37% by the reaction of 1-methylisatoic anhydride (**2**) with diethyl sodiumphosphonate at 140°C [3].



2 **3**

When heated with potassium cyanide the same anhydride gave a 49% yield of 1-methylisatin imine (**4**) [4].



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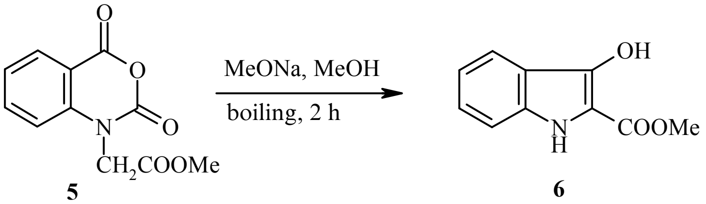
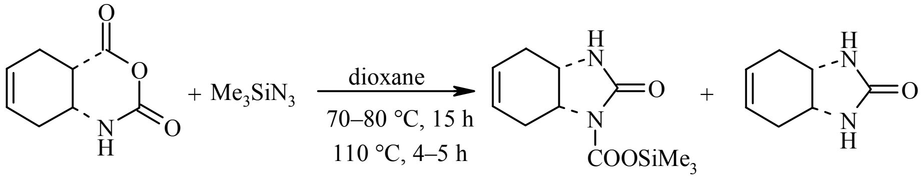
When boiled in methanol in the presence of sodium methoxide the anhydride **5** undergoes recyclization and is converted into the indole derivative **6** with a yield of 89% [5].



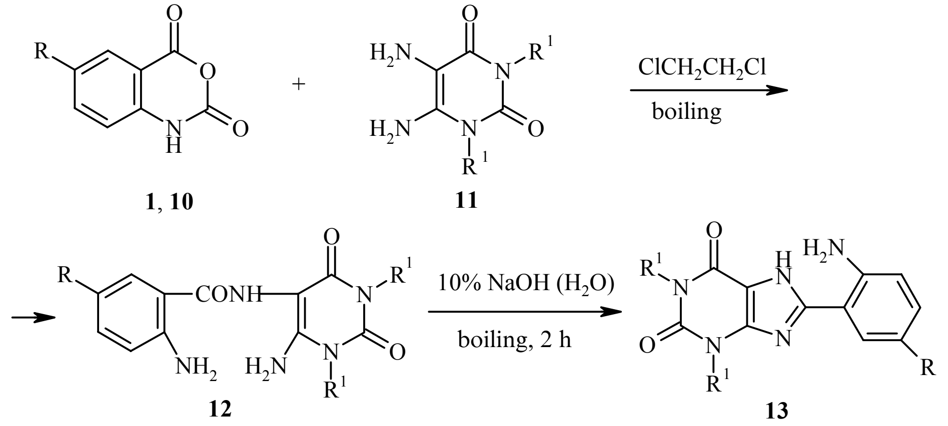
5 **6**

There are also a series of papers on the formation of rings containing two or three nitrogen atoms. For example, the action of heat on *cis*-tetrahydroisatoic anhydride (**7**) with trimethylsilyl azide leads to compounds **8** (yield 37%) and **9** (yield 34%), also having the *cis* configuration [6].



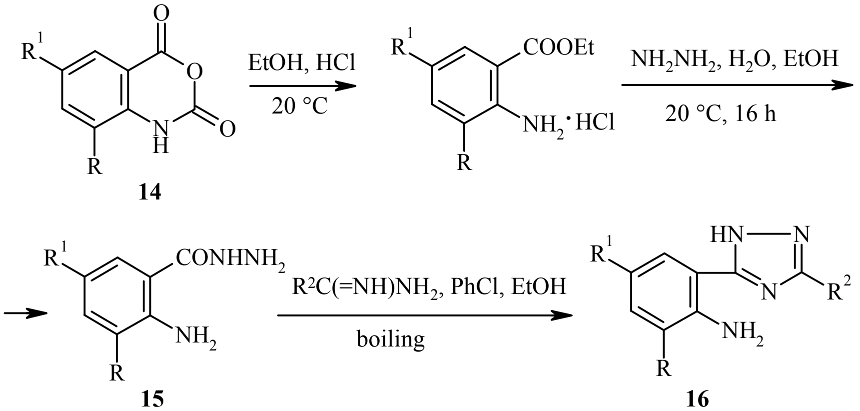
7 **8** **9**

When heated in water in the presence of sodium hydroxide, the products from the reaction of the anhydrides **1** and **10** with the diamine **11**, i.e., the amino amides **12**, undergo cyclization and are converted into the xanthine derivatives **13** with yields of 53-67% [7].



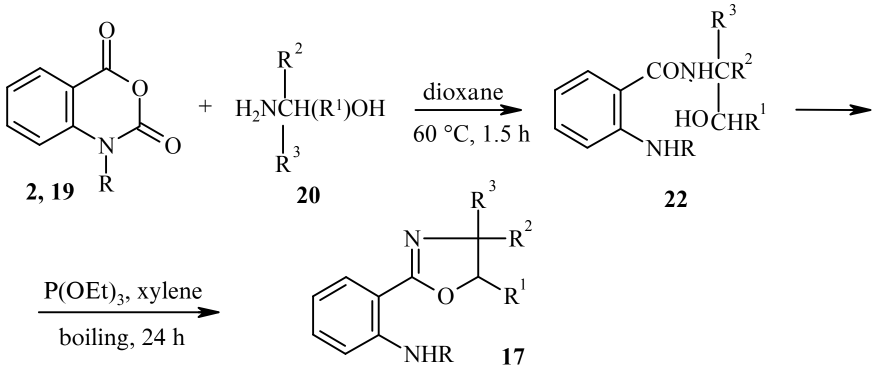
R, R¹ = H, Pr; H, M; Cl, Pr

The action of alcoholic hydrochloric acid on the anhydrides **14** followed by reaction with hydrazine hydrate gave aminohydrazides, the reaction of which with amidines $R_2C(=NH)NH_2$ led to the 3,5-disubstituted 1,2,4-triazoles **16** [8].

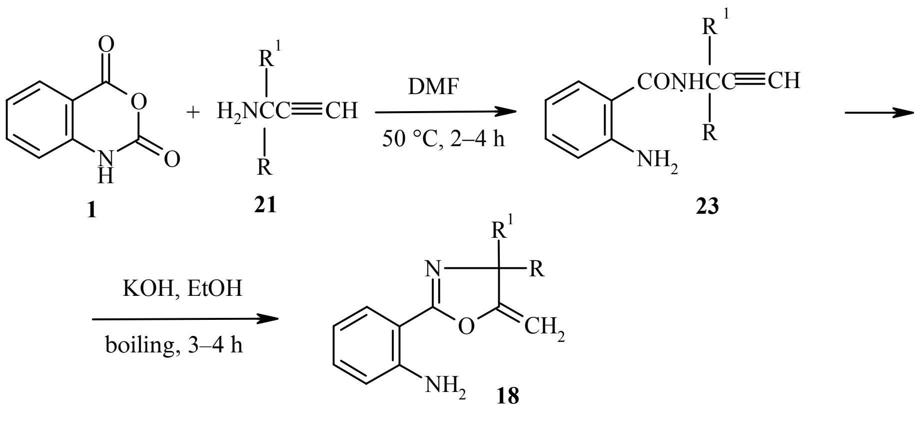


R, R¹, R² = H, Cl, 2-pyridyl; Cl, Cl, Ph

There are also examples of the formation of five-membered rings with two and three different heteroatoms. Thus, syntheses of derivatives of Δ^2-oxazolines **17** (yields 34-87%) and **18** (yields 36-65%) from the anhydrides **2** and **19** and the amines **20** and **21** with isolation of the intermediate amides **22** and **23** respectively were described in [9, 10].

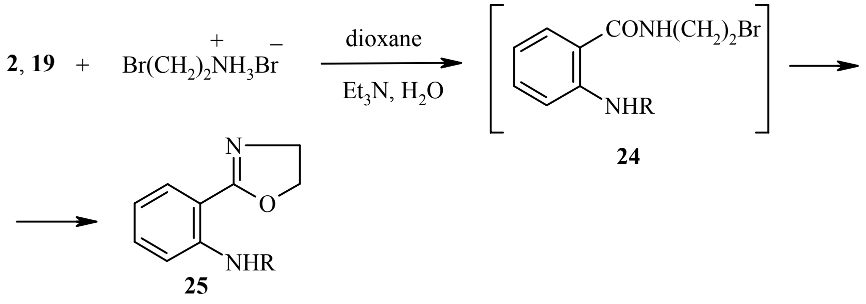


R, R¹, R², R³ = Me, H, H, H; Me, Me, H, H; Me, H, Me, H; Me, H, Me, Me;
$PhCH_2$, Et, H, H; Me, H, Me, $HOCH_2$; Me, Et_2NCH_2, H, H



R, R¹ = Me, Me; Et, Et; $(CH_2)_5$

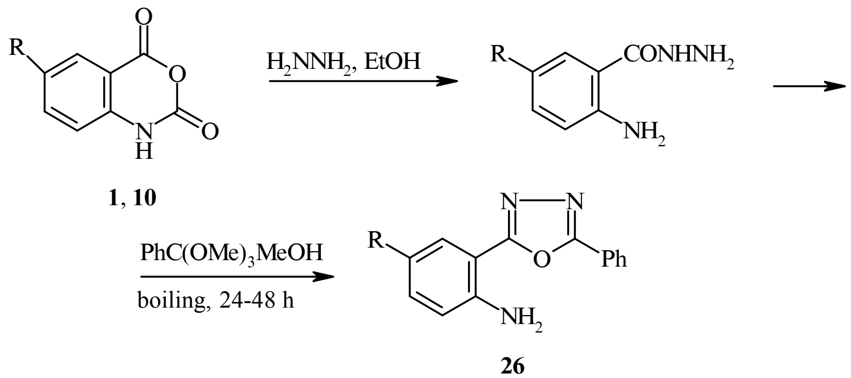
The Δ^2-oxazolines **25** were obtained from the anhydrides **2** and **19** and β-bromoethylammonium bromide through the intermediate compounds **24** [11].



R = Me, Et, Pr, $EtOOCCH_2$

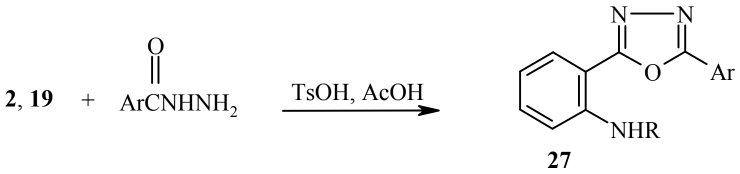
The paths to the production of compounds containing an oxadiazole ring from isatoic anhydrides are more varied. For example, the synthesis of 5-(2-aminophenyl)-3-phenyl-1,2,4-diazole in two stages was patented; a mixture of phenylacetonitrile, hydroxylamine sulfate, and the salt of the dibutylamide of sulfonated oleic acid was kept with an aqueous solution of sodium carbonate at 90°C for 5 h, the anhydride **1** was added, and the reaction mixture was kept at the same temperature with 50% aqueous sodium hydroxide for 1 h [12].

2,5-diaryl-1,3,4-oxadiazoles **26** were synthesized by heating the hydrazides obtained from the anhydrides **1** and **10** and hydrazine with trimethyl orthobenzoate [13].



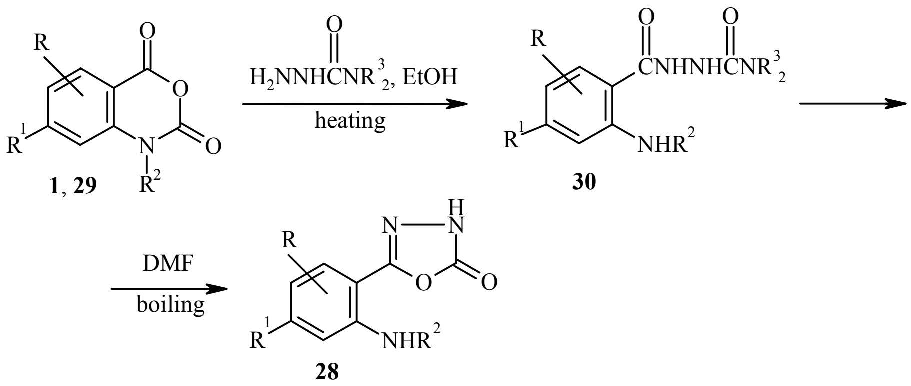
R = H, Cl, Br, Me

The 2,5-diaryl-substituted 1,3,4-oxadiazoles **27** were obtained from the anhydrides **2** and **19** and the hydrazides of aromatic acids in acetic acid in the presence of *para*-toluenesulfonic acid [14].



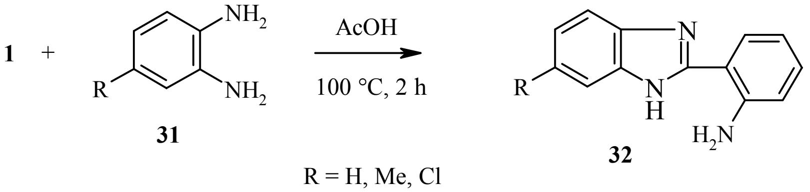
R = Me, Et, $PhCH_2$; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$

2-Aryl-1,3,4-oxadiazol-5(4H)-ones **28** were synthesized with yields of 50-95% by heating the anhydrides **1** and **29** with dimethyl- or diethyl-substituted semicarbazide in alcohol until the release of carbon dioxide had stopped and then boiling the obtained compounds **30** in DMF [15].



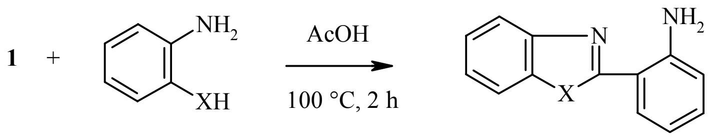
R, R^1, R^2, R^3 = H, H, H, Me; 5-Me,H, H, Me; 5-Cl, H, H, Me; H, H, Me, Me;
H, H, Ph, Me; H, H, 3-$F_3CC_6H_4$, Me; H, H, H, Et; 5-Me, H, H, Et; 4-Cl, H, H, Et

The condensation of isatoic anhydride **1** with the diamines **31** in acetic acid led to the substituted benzimidazoles **32** (yields 62-70%) [16].



R = H, Me, Cl

When *ortho*-aminophenol or *ortho*-aminothiophenol were used in this reaction the analogs of the product **32** (R = H), i.e., compounds (**33)** with two different heteroatoms in the five-membered ring, were obtained with yields of ~70% instead of the diamines **31** [16].



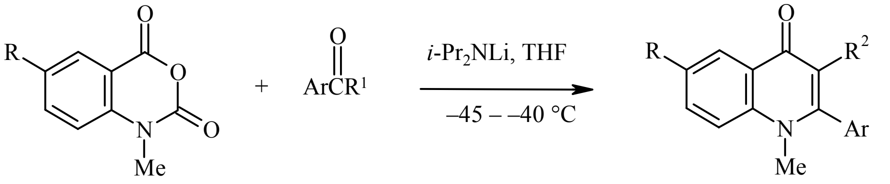
X = O, S **33**

2. REACTIONS LEADING TO THE FORMATION OF SIX-MEMBERED HETEROCYCLES

In contrast to the data presented above, the formation of compounds containing a six-membered heterocycle based on isatoic anhydrides has been discussed very widely in the literature. This has given rise to the need to divides this material into several subsections.

2.1. Reactions Involving the Formation of Six-membered Rings with One Nitrogen Atom

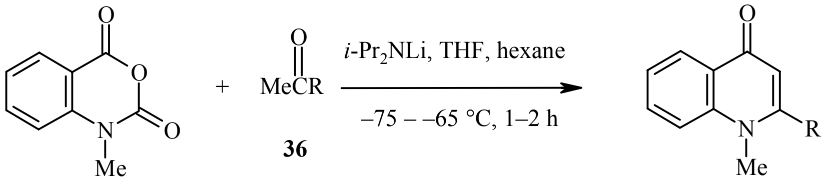
Many examples of the formation of new six-membered rings containing a nitrogen atom in the reaction of isatoic anhydrides with ketones, diketones, various ether derivatives, lactones, and organometallic compounds are known. Thus, the anhydrides **2** and **34** condense with acetophenones and ω-methoxyacetophenones in the presence of lithium diisopropylamide at low temperatures with the formation of derivatives of quinolone **35** [17, 18].



2, **34** → **35**

Ar, R, R^1, R^2, time (h), yield (%): Ph, H, Me, H, 2.5 (81); 3,4-$(OCH_2O)C_6H_3$, H, Me, H, 1.25, (63); Ph, H, $MeOCH_2$, MeO, 3.25, (34); Ph, MeO, Me, H, 25, (70); Ph, MeO, $MeOCH_2$, MeO, 33, (61) [17]; 4-$MeOCH_2OC_6H_4$, H, Me, H, 5, (26) [18]

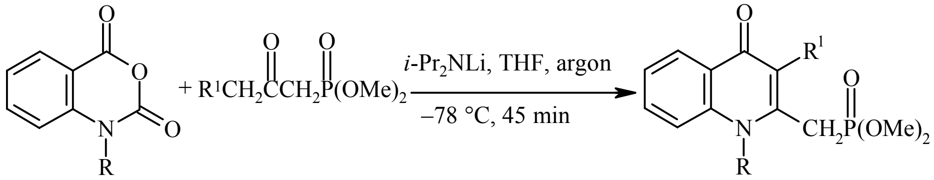
Under analogous conditions, but at a lower temperature (-75 to -65°C), the anhydride **2** reacts with methyl alkyl (alkenyl, alkynyl) ketones **36** at their methyl group with the formation of compounds **37** [19-21].



2 + **36** → **37**

R = $Me(CH_2)_8$, $Me(CH_2)_{10}$, $Me(CH_2)_3C{\equiv}C(CH_2)_7$, $Me(CH_2)_3CH{=}CH(CH_2)_7$ [19]; Et_2CH [21]; $HOCH_2$ [20]

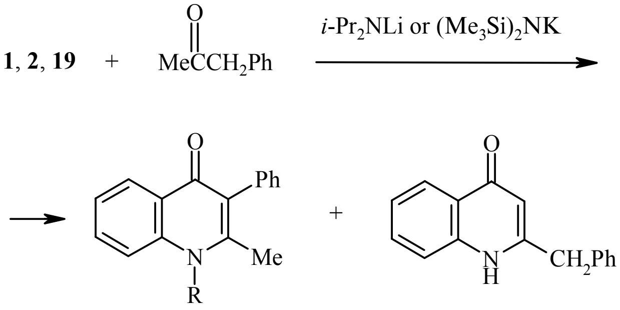
The reaction of the anhydrides **2** and **19** with ketophospholanes $R^1CH_2COCH_2P(O)(OMe)_2$ takes place regioselectively at the terminal methyl or benzyl group of the latter and leads to phospholanes **38** with a quinolone fragment (yields 39-61%) [22].



2, **19** → **38**

R, R^1 = Me, H; Me, Me; Me, i-Pr; Me, Ph; i-Pr, Ph; Ph, H; Ph, Me; Ph, i-Pr

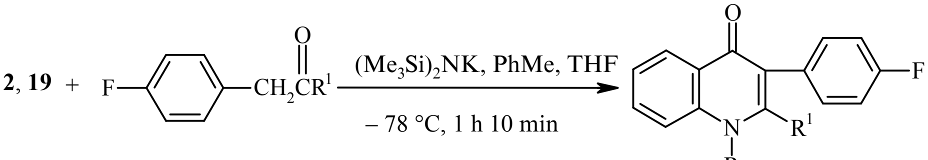
The regioselectivity of the reaction with methyl benzyl ketone depends on the conditions under which it is conducted and on the substituent R at the nitrogen atom of the isatoic anhydride. Thus, after treatment of this ketone with lithium diisopropylamide (-78°C, 1 h), addition of the unsubstituted anhydride **1**, and treatment of the reaction mass between -78°C and 20°C a mixture of compounds **39** (R = H) (yield 30%) and **40** (yield 34%) was obtained. Under analogous conditions, but with briefer treatment of the ketone with lithium diisopropylamide (0.5 h), in both cases only the isomers **39** (with R = Me yield 80%, with R = *i*-Pr yield 82%) were obtained from the anhydrides **2** (R = Me) or (**19**) (R = *i*-Pr). One isomer **39** (R = Me) was also obtained with a yield of 56% when the ketone was treated with potassium bis(trimethylsilyl)amide in toluene and THF in a nitrogen atmosphere (-78°C, 1 h), the anhydride (**2**) in THF was added, and the mixture was kept at -78°C for 5 min [23].



39 **40**

R = H, Me, i-Pr

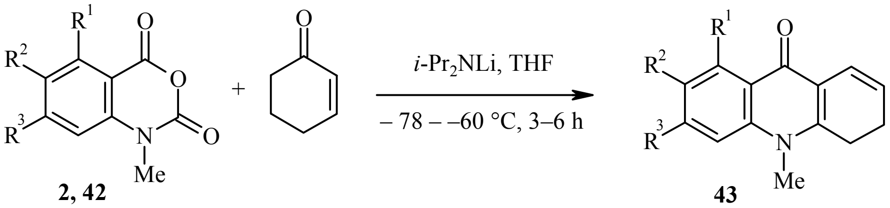
Quinolone derivatives **41** similar to the products **39** are formed with yields of 62 and 83% as a result of the condensation of the anhydrides **2** and **19** with ketones in toluene and THF in the presence of potassium bis(trimethylsilyl)amide [23, 24].



41

R, R¹ = Me, t-BuSiMe$_2$O(CH$_2$)$_3$ [23]; Me, Me; i-Pr, Me [24]

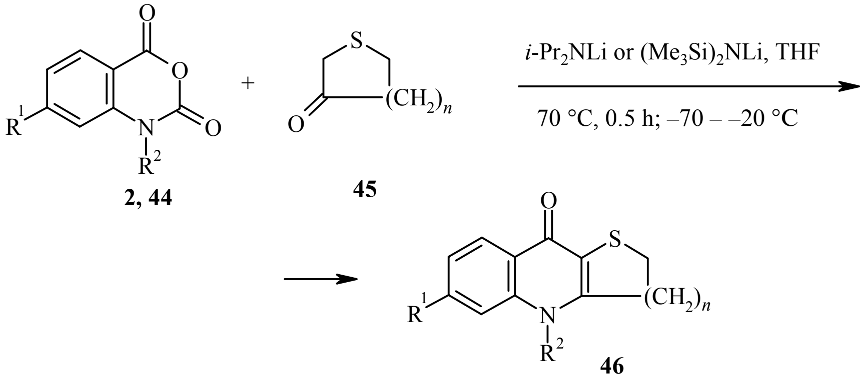
The reaction of isatoic anhydrides with cyclic ketones and diketones leads to condensed tri- and tetracyclic compounds. For example, the reaction of the anhydrides **2** or **42** with cyclohexen-2-one in the presence of lithium diisopropylamide gave 28-49% yields of the acridine derivatives **43** [25].



2, 42 **43**

R¹, R², R³ = H, H, H; MeO, MeO, MeO; MeO, –OCH$_2$O–,

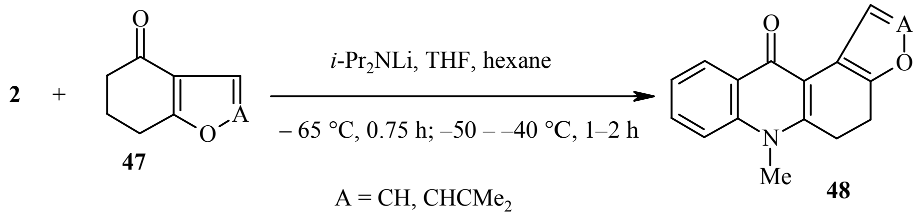
Products **46** with two condensed heterocycles are formed (with yields of 24-80%) from the anhydrides **2** or **44** and thiacyclanones **45** in the presence of lithium diisopropyl- or bis(trimethylsilyl)amides [26].



2, 44 45 46

R^1, R^2 (n) = H, Me (1); H, Me(2); H, Me (3); F, Me (3)

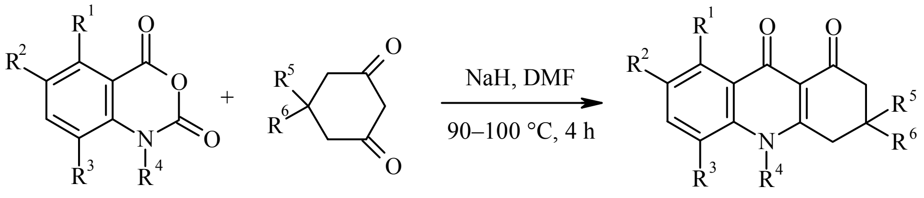
The condensation of the anhydride **2** with bicyclic ketones of the heterocyclic series **47** under the influence of lithium diisopropylamide leads to angularly constructed compounds **48**, also containing two heterocyclic rings in the molecule [27, 28].



47 48

A = CH, $CHCMe_2$

The tricyclic linear products **49** are formed with yields of 8-70% as a result of the reaction of the anhydrides (**1**) and **50** with 1,3-cyclohexanedione and its derivatives **51** in the presence of sodium hydride at 90-100°C [29, 30].

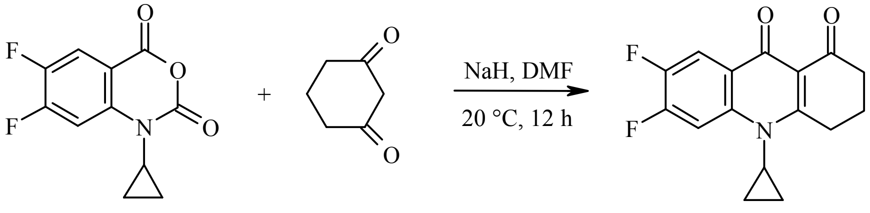


1, 50 51 49

R^1 = H, Cl; R^2 = H, F, Cl, Br, I, O_2N, Et, MeO, F_3C; R^3 = H, Cl, Br;
R^4 = H, Me, Et, Bu, C_6H_{13}, CH_2=$CHCH_2$; R^5 = H, Me; R^6 = Me, i-Pr, 4-$F_3CC_6H_4$,
2-ClC_6H_4, 4-$C_6H_{11}C_6H_4$, 2,4-$Cl_2C_6H_3$, 3,4-$Cl_2C_6H_3$, 4-pyridyl, 4-$MeSC_6H_4$,
4-$O_2NC_6H_4$, 2-pyridyl, 4-Cl-3-$F_3CC_6H_3$

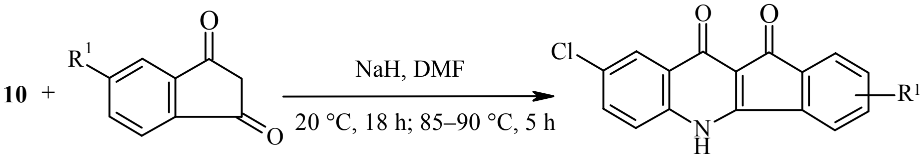
In the reaction of the diketone **51** ($R^5 = R^6$ = Me) with the anhydride **1** (i-Pr_2NLi, 80°C, 4 h) the yield of compound **49** ($R^1 = R^2 = R^3 = R^4$ = H, $R^5 = R^6$ = Me) amounted to 83% [31].

Another example of the construction of a tricyclic condensed system with a nitrogen-containing six-membered heterocycle is the reaction of the anhydride **52** with 1,3-cyclohexanedione in the presence of sodium hydride, as a result of which compound **53** was obtained with a yield of 74% [32].



52 **53**

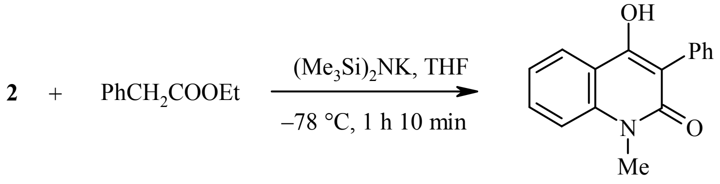
The tetracyclic compounds **54** with a linear condensed structure were synthesized with yields of 58% (R' = H) and 82% (R' = Cl) by the condensation of the anhydride **10** (R = Cl) with 1,3-indandiones **55** under the influence of sodium hydride [33].



55 **54**

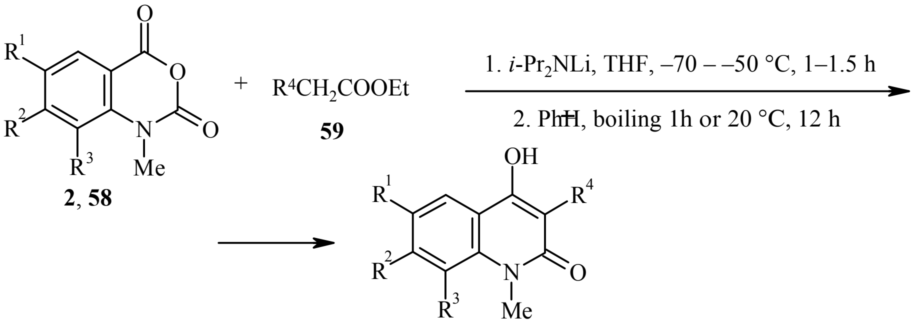
R^1 = H, Cl

4-Hydroxy-1-methyl-3-phenyl-2-quinolone (**56)** is formed with a yield of 80% as a result of the reaction of the anhydride **2** with ethyl phenylacetate in the presence of potassium bis(trimethylsilyl)amide at -78°C [34].



56

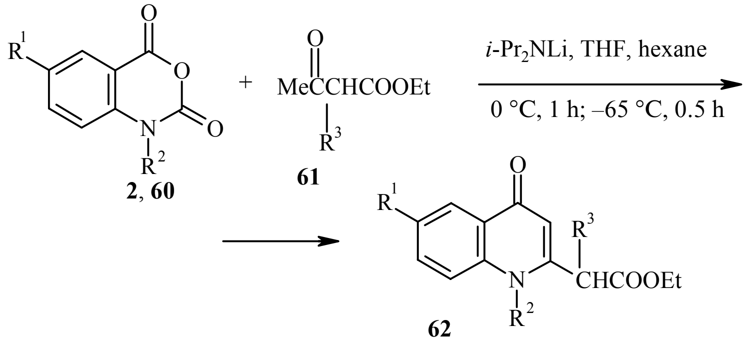
A group of derivatives of 4-hydroxy-1-methyl-2-quinolone (**57**) (yields 45-80%) were synthesized by the reaction of the anhydrides **2** and **58** with the products from treatment of the carboxylic esters **59** with lithium diisopropylamide (THF, from -70 to -50°C, 1-1.5 h) [35, 36].



57

R^1, R^2, R^3, R^4 = H, H, H, H; H, H, H, Me; H, H, H, MeS; H, H, H, $Me_2C{=}CHCH_2$;
H, H, MeO, $Me_2C{=}CHCH_2$; MeO, MeO, H, $Me_2CCH{=}CH_2$ [35]; H, H, H, MeO;
H, H, MeO, MeO [36]

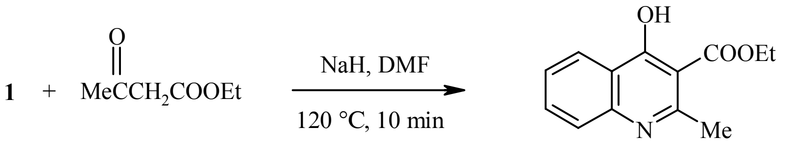
The anhydrides **2** and **60** react with the keto esters **61** under the influence of lithium diisopropylamide at the methyl group of **61**, and the 4-quinolone derivatives **62** are formed with yields of 41-64% [37].



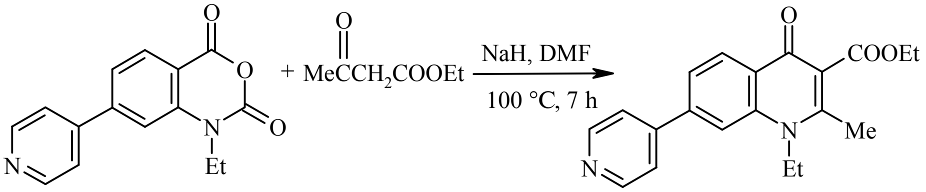
2, **60** **61** **62**

R^1, R^2, R^3 = H, Me, H; Cl, H, Me; H, $MeOCO(CH_2)_2$, H; H, H, $4\text{-}FC_6H_4CH_2$; H, Me, Me;

However, the condensation of the anhydrides **1** or **63** with ethyl 3-oxobutyrate in the presence of sodium hydride takes place at the methylene and not the methyl group of the ester, leading to the products **64** (yield 71%) [38] or **65** (yield 29%) [39] respectively.



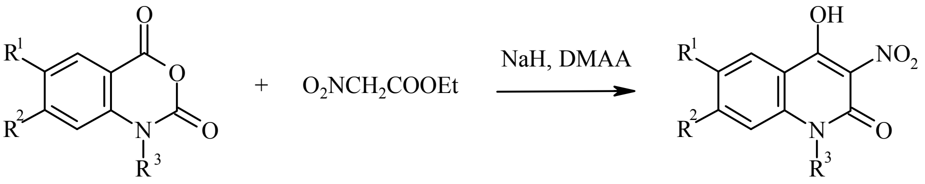
64



63 **65**

The reaction of the anhydride **1** with the ester $OCNCH_2COOEt$ in the presence of diazabicycloundecene in THF followed by treatment of the reaction mixture with concentrated hydrochloric acid in methanol gave 3-amino-4-hydroxy-2-quinolone [40].

A series of derivatives of 4-hydroxy-3-nitro-2-quinolone (**66**) were synthesized by the reaction of the anhydrides **29** with ethyl nitroacetate in the presence of sodium hydride in dimethylacetamide (DMAA) at 120°C (5 or 18 h) [41, 42] or at 170°C (2 h) [43].

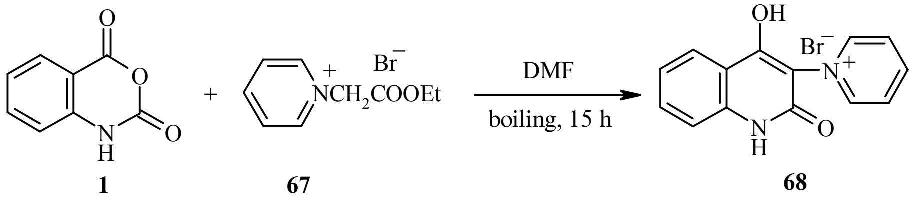


29 **66**

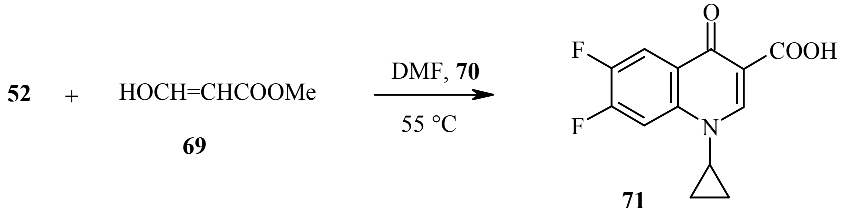
R^1, R^2, R^3 = H, H, Bu [41]; H, H, HC≡CCH_2; H, H, $PhCH_2$; Me, Me, Me;

MeO, MeO, $Me_2C{=}CHCH_2$; H, H, cyclopropylmethyl; Me, Me, $CH_2{=}CHCH_2$;
MeO, MeO, $CH_2{=}CHCH_2$; $–OCH_2O–$, $CH_2{=}CHCH_2$, [42]; H, H, Ph (yield 89%) [43]

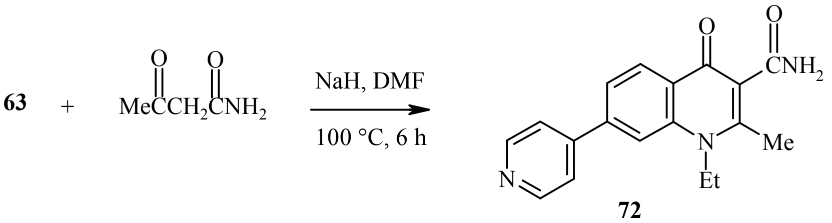
Compound **68** was obtained with a yield of 41% by boiling a mixture of the anhydride **1** with the pyridinium salt **67** in DMF [44].



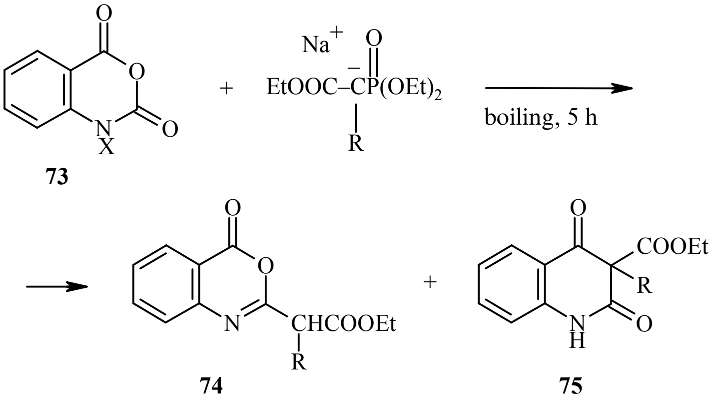
The ester of the enolic form of formylacetic acid (**69**) reacts with the anhydride **52** in the presence of N,N[1]-dimethylimidazolidinone (**70**) to form 3-carboxy-1-cyclopropyl-6,7-difluoro-4-quinolone (**71**) [45].



The condensation of the anhydride **63** with acetoacetamide under the influence of sodium hydride leads to compound **72** (yield 35%) [46].

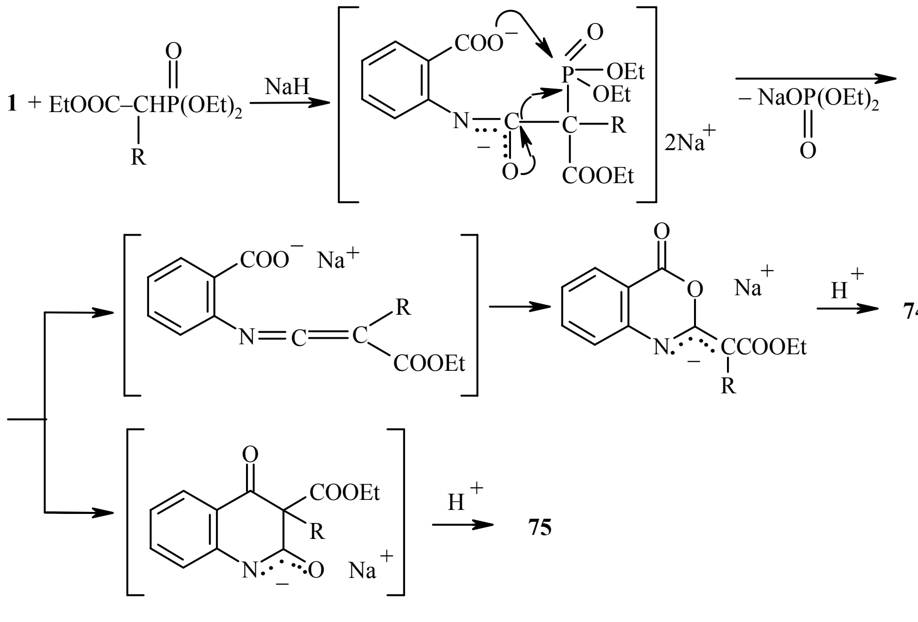


The reaction of the anhydride **1** with the previously prepared sodium derivative of the phosphonate ester **73** (R = Me) gives a mixture of the benzoxazinone **74** and quinolinedione **75**, the ratio and yields of which depend on the solvent used for the reaction. If the reactions of compounds **73** (R = Me, Et, CH_2=$CHCH_2$, $PhCH_2$) are carried out with the previously prepared sodium derivative of the anhydride **1**, only compounds **75** are formed [47].

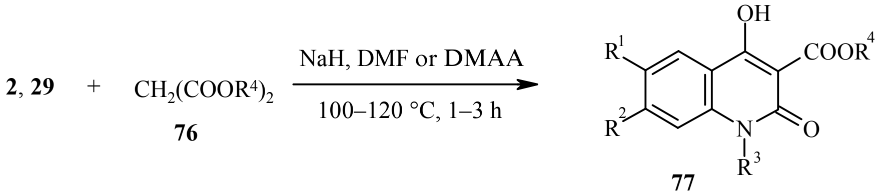


R, X, solvent, [yield of compounds **74** and **75**, %]: Me, H, PhH, (64 and 4);
Me,H, DMF + PhH, (18 and 43); Me, Na, DMF + PhH, (0 and 60); Et, Na, DMF + PhH, (0 and 50);
CH_2=$CHCH_2$, Na, DMF + PhH, (0 and 69); $PhCH_2$, Na, DMF + PhH, (0 and 20)

The authors propose the following scheme for the formation of compounds **74** and **75** [47]:

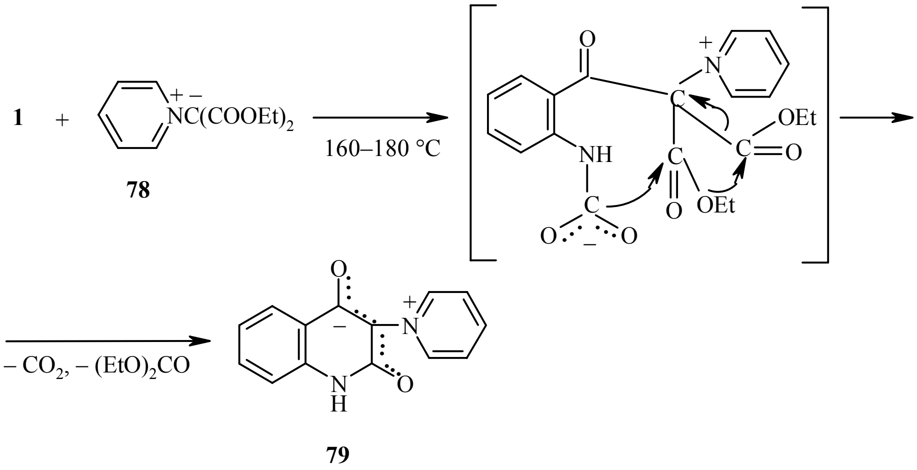


The derivatives of 4-hydroxy-2-quinolone (**77**) (yields 27-90%) were synthesized by heating the anhydrides **2** or **29** with malonic esters **76** in the presence of sodium hydride [46, 48-50].

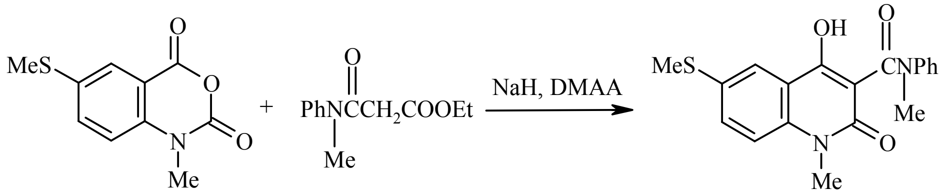


R^1, R^2, R^3, R^4 = H, 4-pyridyl, Et, Et [46]; H, H, Me, Et; MeO, MeO, CH_2=$CHCH_2$, Et; H, H, Me, $PhCH_2$; MeO, MeO, CH_2=$CHCH_2$, $PhCH_2$; H, H, Me, *t*-Bu; MeO, MeO, CH_2=$CHCH_2$, *t*-Bu [48]; H, H, C_6H_{13}, Et [49]; H, H, Bu, Et (16 h) [50]

The reaction of the ylide **78** with anhydride **1** under the influence of heat leads to the release of CO_2 and $(EtO)_2C$=O, and pyridinium ylide **79** is formed with a yield of 53% [42].



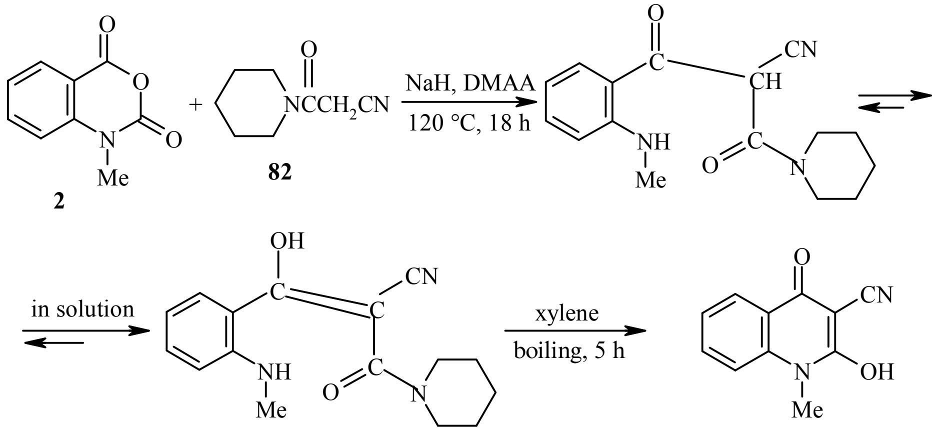
The quinolone derivatives **81** are formed when 1-methyl-6-methylthioisatoic anhydride and malonamic ester (**80**) are treated with sodium hydride [51].



80 **81**

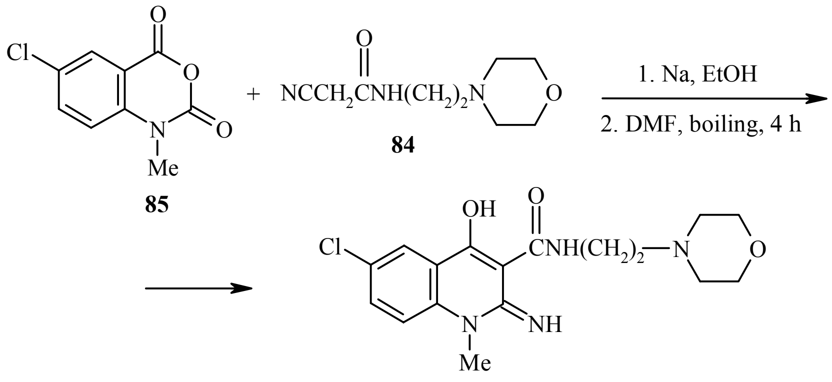
The reaction of the anhydride **1** and methyl cyanoacetate in DMF in the presence of triethylamine, followed by heating the reaction product with sodium hydroxide, leads to 3-cyano-2,4-dihydroxyquinoline [52].

When treated with sodium hydride the anhydride **2** and cyanoacetylpiperidine **82** condense with the formation of the product **83** (yield 59%), which undergoes cyclization when boiled in xylene to 3-cyano-2-hydroxy-1-methyl-4-quinolone (yield 66%) [53]



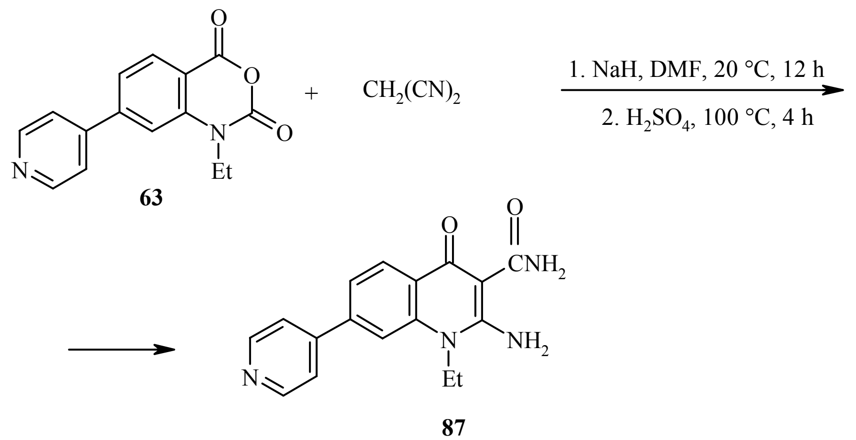
2 **82** **83**

Compound **86** is formed with a yield of 42% after the reaction of the cyanoacetamide (**84**) with sodium ethoxide, the addition of the anhydride **85**, and boiling [54].



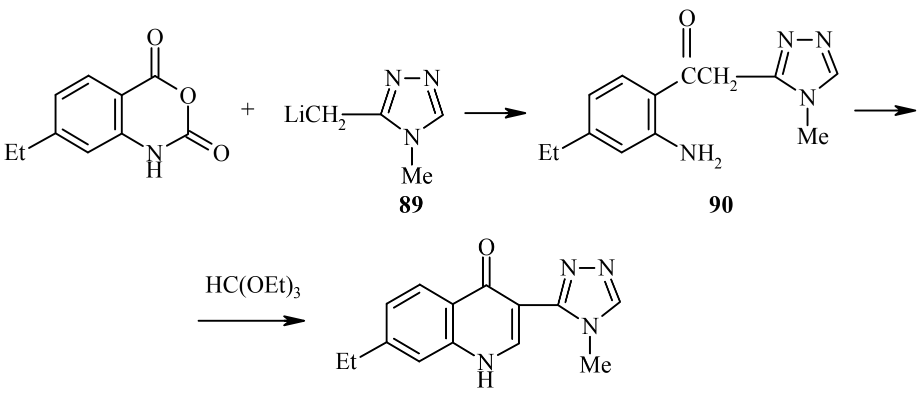
85 **84** **86**

The condensation of the anhydride (**63**) with malononitrile in the presence of sodium hydride followed by heating with sulfuric acid gave the quinolone **87** (yield 38%) [46].



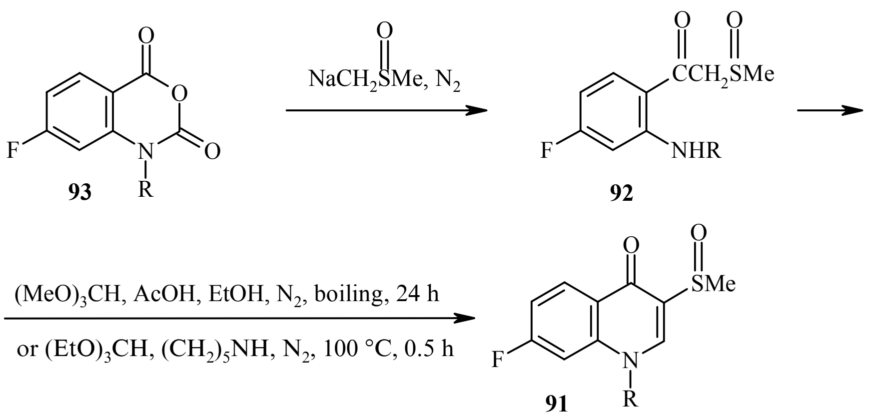
87

The patent [55] describes a two-stage synthesis of the 4-quinolone derivative **88**, involving treatment of 7-ethylisatoic anhydride with the lithium derivative **89** and cyclization of the obtained ketone **90** using orthoformic ester.



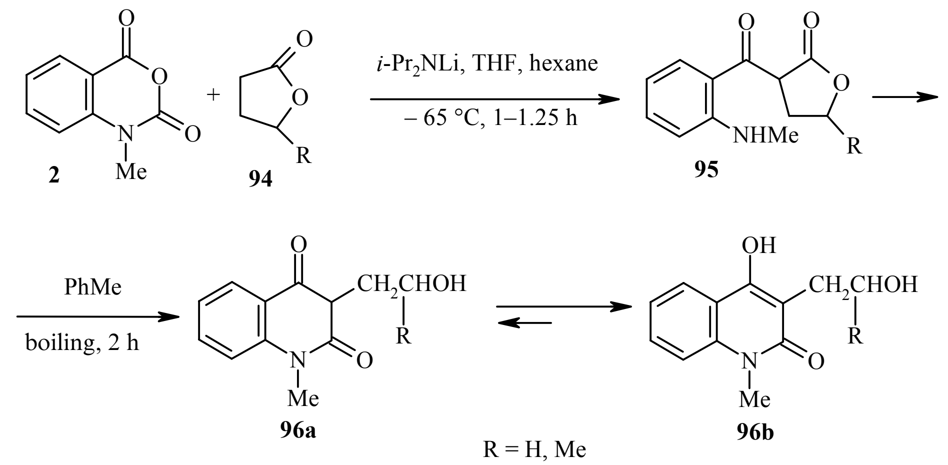
88

Two versions of a similar method for the production of compound **91** were proposed in [56]. In one the ketones **92** formed from the anhydrides **93** were boiled with methyl orthoformate in acetic acid. (With R = H the yield was 79%, and with R = Me it was 70%.) In the other these ketones were heated with ethyl orthoformate in the presence of piperidine. (With R = H the yield was 52%.)

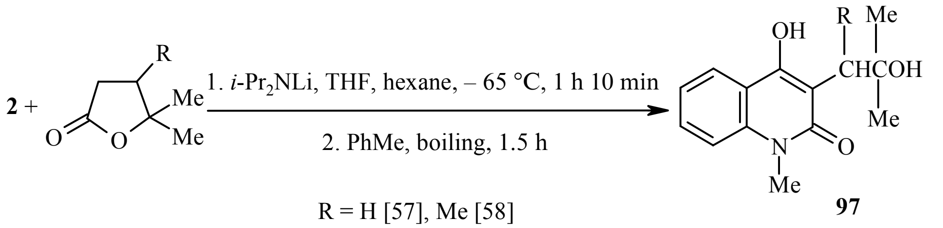


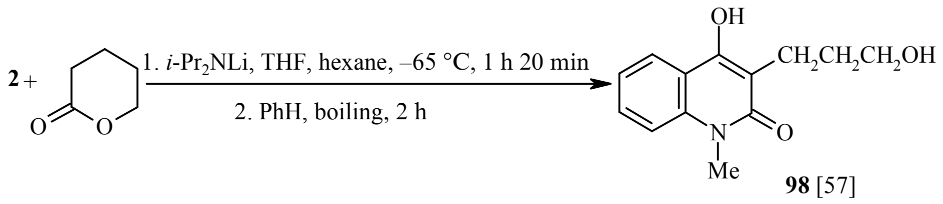
R = H, Me

A method was developed for the synthesis of quinoline derivatives from isatoic anhydrides and lactones. The amino ketones formed at the first stage were then converted into the desired products by cyclocondensation after isolation or by direct heating of the reaction mass. Thus, the reaction of the anhydride **2** with the butyrolactones **94** in the presence of lithium diisopropylamide gave the amino ketones (**95**) (yield 99%), which when boiled in toluene gave 4-hydroxy-3-R-1-methyl-2-quinolones **96** (yield 98% with R = H or 70% with R = Me). It was established that the latter exist in two isomeric forms **96a**,**b** [57].

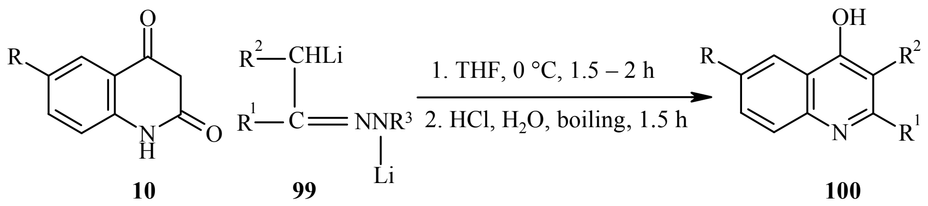


The alcohols **97** (yield 84%) and **98** (yield 38%) were obtained similarly from the anhydride **2** and 2,2-dimethyl- or 2,2,3-trimethylbutyrolactone (boiling in benzene or toluene) [57, 58].



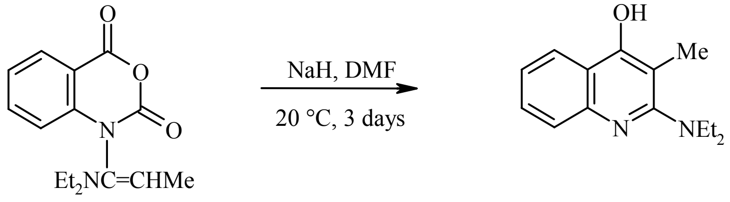


The 4-hydroxyquinolines **100** are formed by reacting the anhydrides **10** with the dilithium derivatives of the hydrazones **99** at 0°C and heating the reaction mixtures with hydrochloric acid [59].



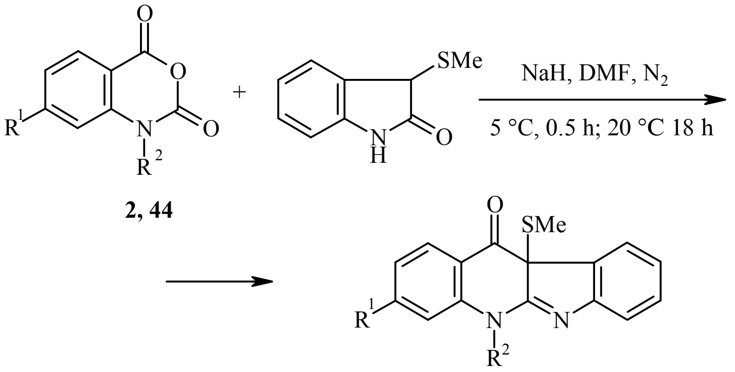
R, R^1, R^2, R^3, (yield, %): Cl, $(CH_2)_5$, MeOCO, (36); Cl, $(CH_2)_6$, MeOCO, (42); Cl, $(CH_2)_{10}$, MeOCO, (9); Cl, 4-ClC_6H_4, H, PhCO, (28); Cl, 4-$MeOC_6H_4$, Me, PhCO, (70); H, 4-ClC_6H_4, Me, PhCO, (26); Cl, 4-MeC_6H_4, Me, PhCO, (24)

An example of the direct transformation of the isatoic anhydride **101** into 2-diethylamino-4-hydroxy-3-methylquinoline (yield 48%) by the action of sodium hydride is known [60]



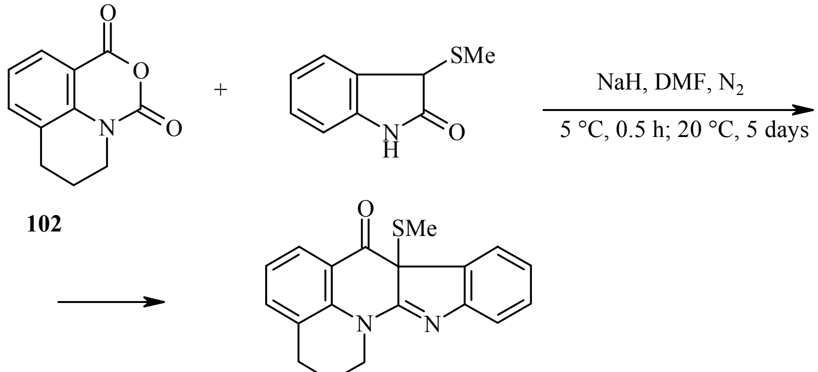
101

The anhydrides **2**, **44**, or **102** react with 3-methylthio-2-indolone to form the tetracyclic compounds **103** (yields 17-53%) or **104** (yields 9%), containing condensed five- and six-membered nitrogen-containing rings [61].



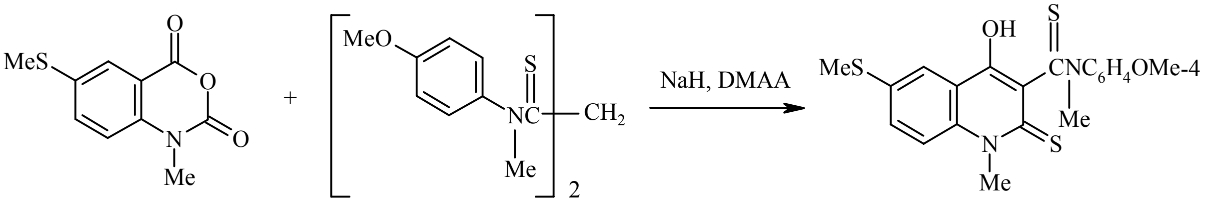
2, 44 **103**

R^1, R^2 = H, Me; Cl, Me; MeO, Me; H, CH_2=$CHCH_2$; H, 4-FC_6H_4



102 **104**

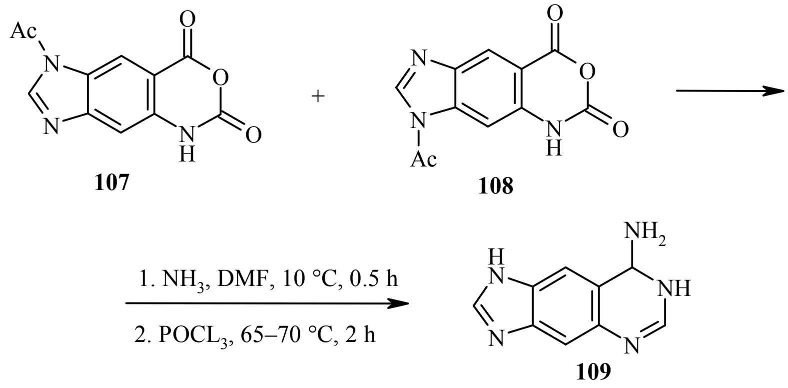
The reaction of 6-methyl-1-methylisatoic anhydride with the dithione **105** in the presence of sodium hydride leads to a derivative of 4-hydroxy-2-quinolinethione **106** [62].



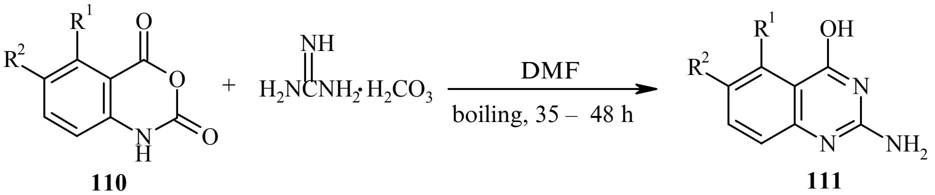
105 **106**

2.2. Reactions Involving the Formation of Six-membered Rings with Two Nitrogen Atoms

The reactions of isatoic anhydrides with various nitrogen-containing compounds of the acyclic, alicyclic, and heterocyclic series leading to derivatives of quinazoline have been studied most widely. Here two approaches to the synthesis of compounds of this group were developed: 1) The initially formed derivatives of anthranilic acid were converted *in situ* into the heterocyclic compounds; 2) the derivatives were isolated and cyclized separately into the required products. For example, the amino derivative **109** was obtained with a yield of 56% by the first method with the action of ammonia followed by phosphorus oxychloride on a mixture of the anhydrides **107** and **108** [63].

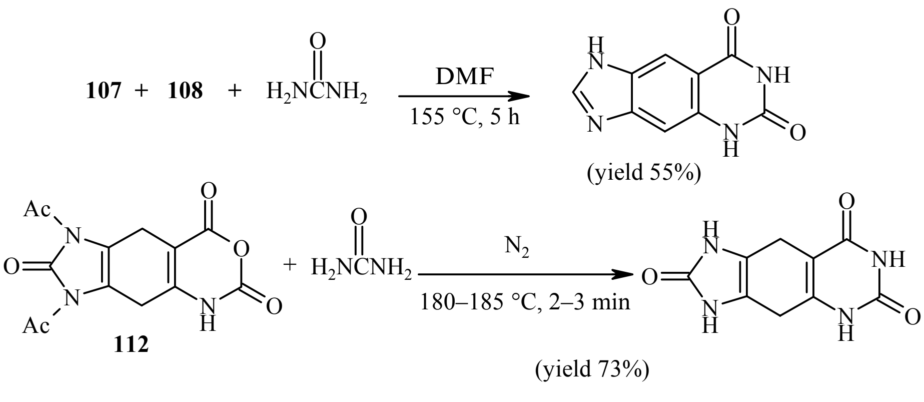


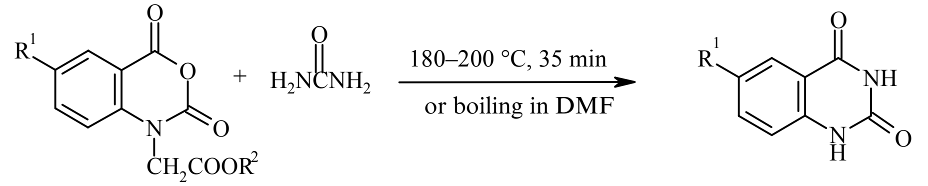
The derivatives of 2-amino-4-hydroxyquinazoline (**111**) were obtained as a result of prolonged boiling of anhydrides **110** with guanidine carbonate in DMF [64, 65].



R^1, R^2, (yield %): H, O_2N, (75); F_3C, H, (44)

The condensation of anhydrides **107**+**108** [63], **112** [66], or **113** [67] with urea was carried out either by heating without a solvent [66, 67] or by boiling in DMF [63, 67].

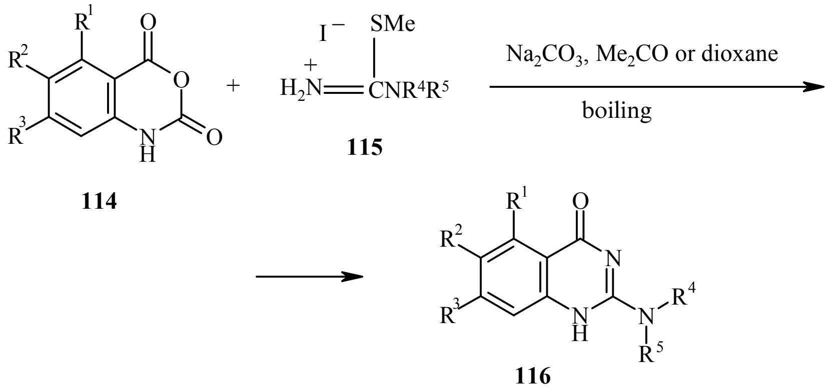




113

R^1, R^2, (yield %): H, Me, (31, in DMF–65); H, Et, (28, in DMF–62); Br, Me, (0, in DMF–45)

When anhydrides **114** are boiled with S-methylisothioureas **115** in acetonitrile [68] or in dioxane [6, 69] in the presence of sodium carbonate the substituted aminoquinazolines **116** are formed (yields 34-100%).

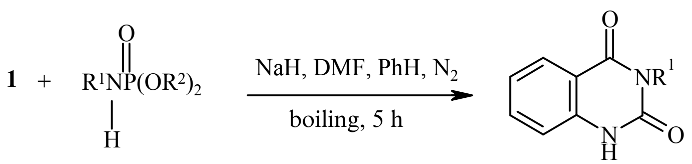


114 115 116

R^1, R^2, R^3,R^4, R^5, (time, h): H, MeO, MeO, H, H, (1.25); H, MeO, MeO, H, Me, (2.0);
H, MeO, MeO, Me, Me (14.0); H, MeO, MeO, Pr, Pr, (61.0); MeO, MeO, H, H, H, (2.5);
MeO, MeO, H, H, Me, (2.75); MeO, MeO, H, Me, Me, (6.0); MeO, MeO, H, Pr, Pr, (12.0) [68];
H, H, H, Pr, Pr, (14.0) [69]

The production of 2-(2-hydroxyphenylamino)-4-quinazolone by condensation of anhydride **1** with N-(2-hydroxyphenyl)thiourea was reported in [70].

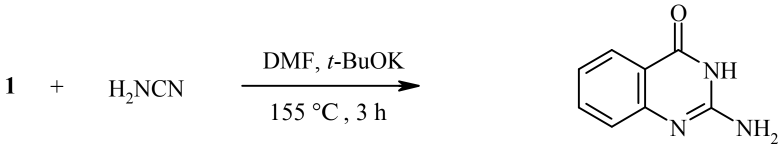
The quinazoline-2,4-dione **117** substituted at position 3 is formed as a result of the reaction of the anhydride **1** with phosphoramidic esters **118** with heat in the presence of sodium hydride [47]



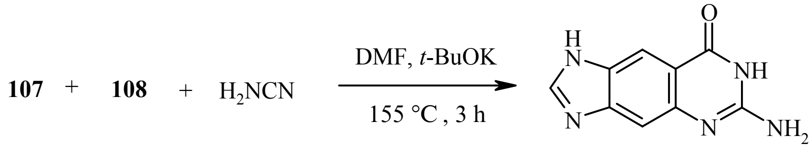
118 117

R^1, R^2, (yield %): Ph, Et, (70); 4-ClC_6H_4, Et, (99);
cyclohexyl, Et, (40); Bu, Me, (31 with boiling for 10 h)

The amino derivatives **119** and **120** were obtained by treating the anhydrides **1** and **107**+**108** respectively with cyanamide at 155°C in the presence of potassium *tert*-butoxide [60].

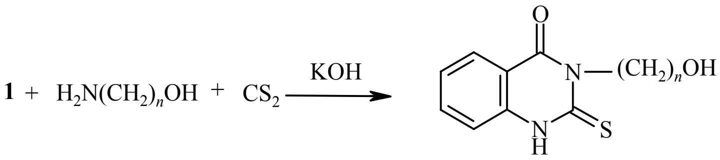


119 (55%)



120

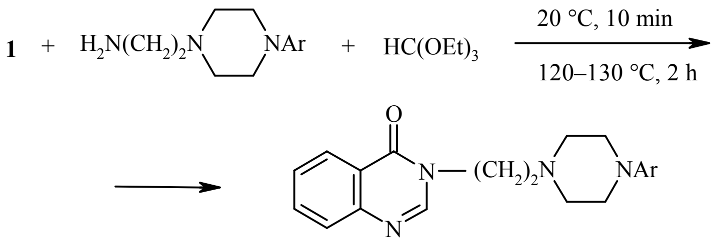
In the reaction of the anhydride **1** with amino alcohols and carbon disulfide in the presence of potassium hydroxide compounds **121** are formed with 75-79% yields [71, 72].



121

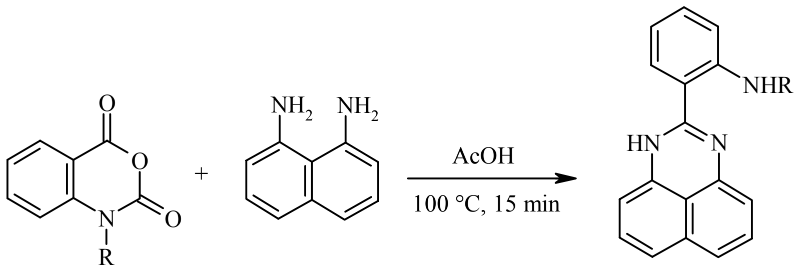
n: 2 [71], 3 [72]

The 4-quinazolone derivative **123** was synthesized with a yield of 99% by heating the anhydride with the amine **122** and ethyl orthoformate [73].



Ar = 2-EtOC$_6$H$_4$ **123**

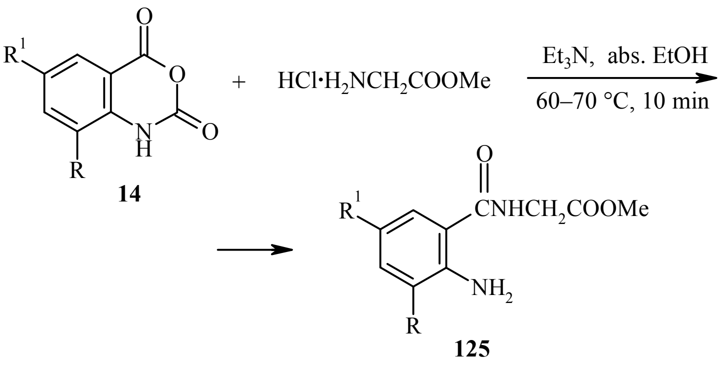
Derivatives of perimidine **124** were obtained with yields of 73-80% by heating the anhydrides **1** and **19** with 1,8-diaminonaphthalene in acetic acid [74].



1, **19** **124**

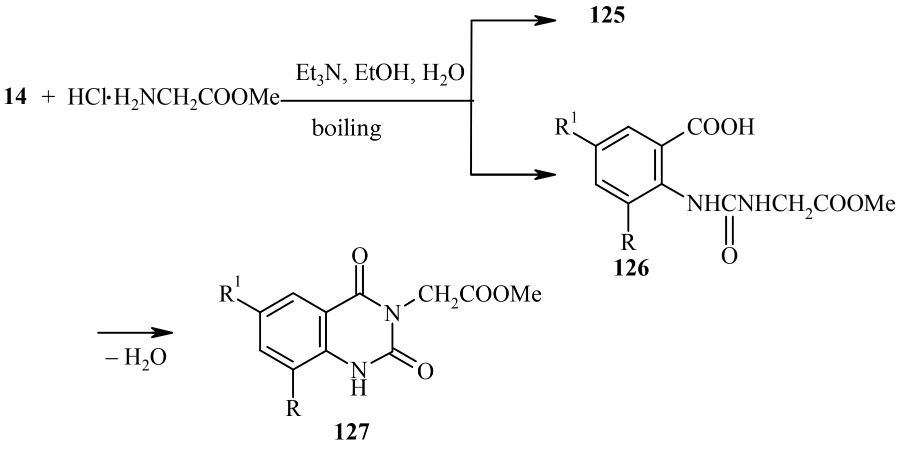
R = H, Me, Et, Ph

In the reaction of glycine methyl ester hydrochloride with the anhydrides **14** in absolute ethanol in the presence of triethylamine the anhydrides are attacked by the amino ester at position 4, and the 2-aminohippuric esters **125** are formed [75].



R, R[1], (yield , %): Br, Br,(90); Cl, Cl, (64)

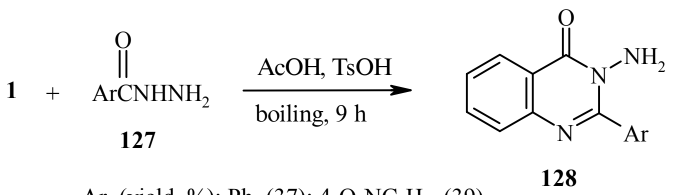
However, when this reaction is carried out in aqueous ethanol positions 2 and 4 of the anhydrides are attacked, leading to the esters of 2-aminohippuric **125** and 2-ureidobenzoic **126** acids, which undergo cyclization under the reaction conditions leading to the uracils **127** [75].



R, R[1], (yield of compounds **126** and **127** %): Br, Br, (23 и 51); Cl, Cl, (21 и 57)

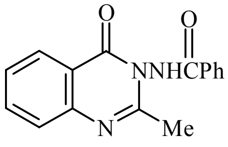
Treatment of the anhydride **1** with *p*-toluamide at 190°C for 1.75 h leads to the formation of 2-(*p*-tolyl)-4-quinazolone [76].

The condensation of the anhydride (**1**) with the hydrazides of arenecarboxylic acids **127** in the presence of p-toluenesulfonic acid gave the 2-aryl-3-amino-4-quinazolones **128** [77].



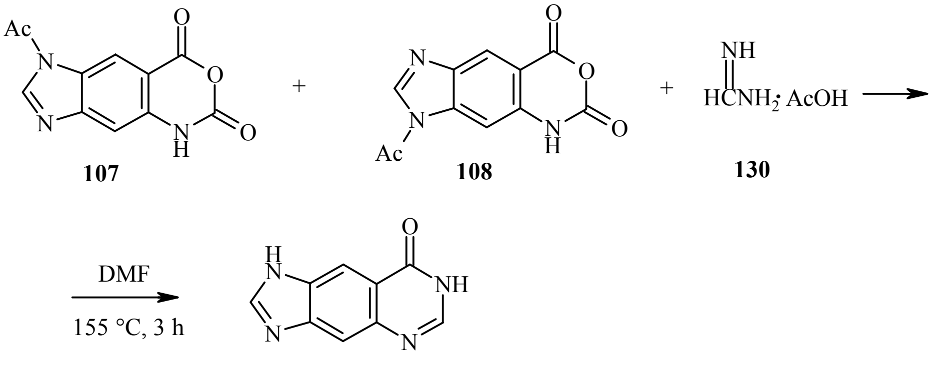
Ar, (yield, %): Ph, (37); 4-$O_2NC_6H_4$, (39)

According to data in [78], the N-carbamoyl derivative **129**, i.e., the product from the reaction of the anhydride **1**, the hydrazide $PhCONHNH_2$, and acetic acid, is also formed with a yield of 19% under these conditions in addition to the N-amino-substituted **128** (Ar = Ph).



129

Formamidine acetate **130** reacts with the anhydrides **107**+**108** in DMF at 155°C [63], with the anhydride **1** [66] or the anhydride **131** [66] when boiled in ethanol, with the anhydride **132** [66] when boiled in methylcellosolve, and with the anhydride **112** [66] at 100°C in N-methylpyrrolidone, and the products **133-137** are formed with yields of 86, 81, 62, 36, and 60% respectively.



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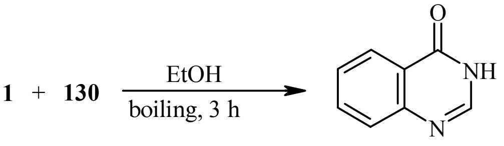

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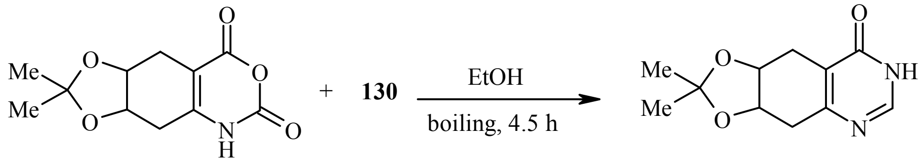
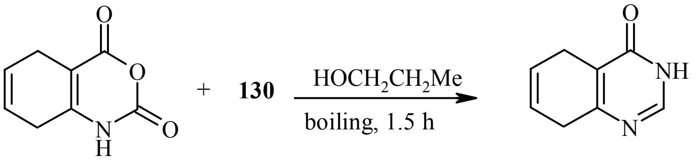
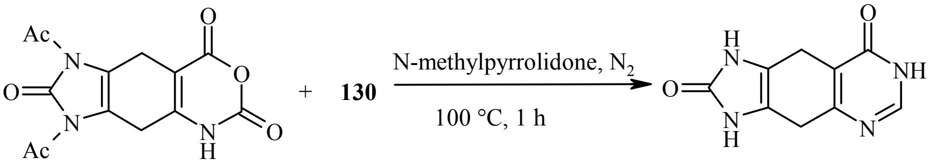


131 **135**

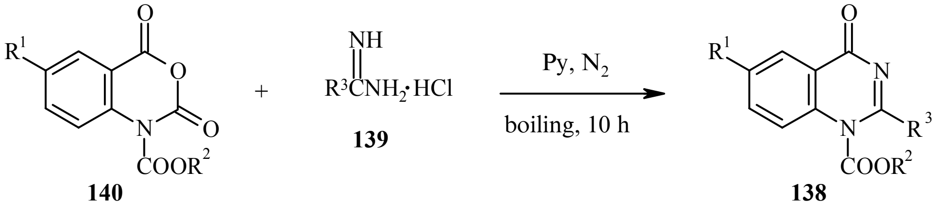


137 **136**



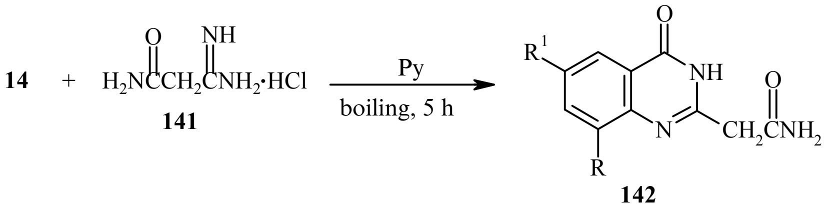
112 **137**

The derivatives of 4(1)-quinazolinone **138** are formed with yields of 58-63% when the amidine hydrochlorides are boiled with the anhydrides **140** in pyridine [79].



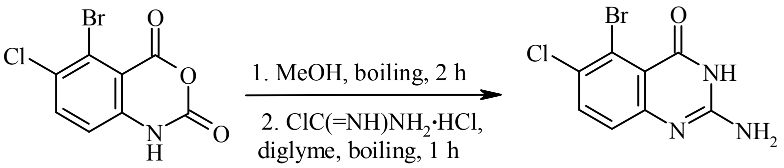
R^1, R^2, R^3: H, Me, 4-HOC_6H_4; H, Et, Ph

The derivatives of 4(3H)-quinazolinone **142** (yields 22-81%) were obtained by boiling the anhydride **14** and the amidine **141** in pyridine [80].

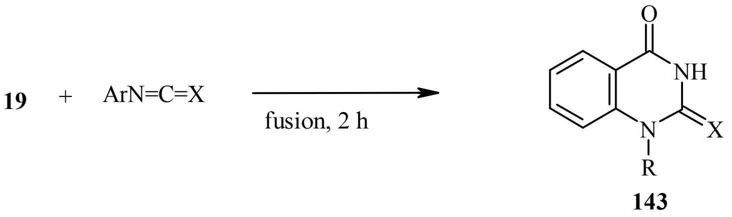


R, R^1: H, H; H, Br; H, Cl; Br, Br; Cl, Cl; H, O_2N

Successive treatment of 5-bromo-6-chloroisatoic anhydride with boiling methanol and then with chloroformamidine hydrochloride in boiling diglyme led to 2-amino-5-bromo-6-chloro-4(3H)-quinazolinone with a yield of 67% [81]

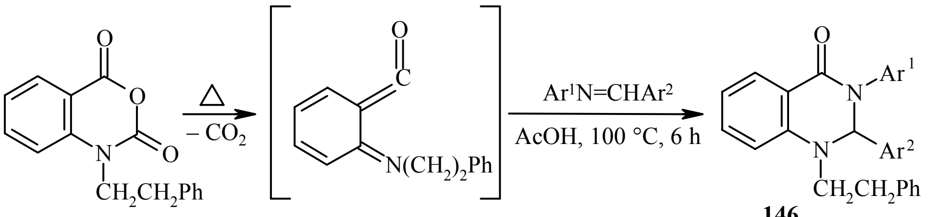


The derivatives of quinazolinedione and thioxoquinazolinone **143** are formed with yields of 70-80% as a result of the fusion of the anhydrides **1** and **19** with isocyanates and isothiocyanates [82].



R = H, Me, Et; Ar = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$; X = O, S

The iminoketene **144**, released when the anhydride **145** is heated, enters into [4+2] cycloaddition with azomethines, leading to the dihydroquinazolinones **146** (yields 53-65%) [83].

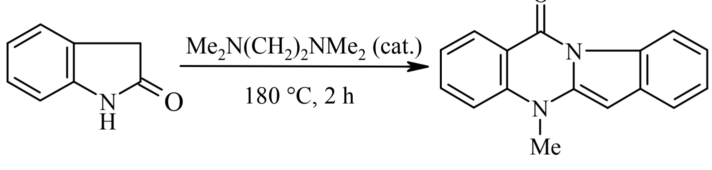


145 **144** **146**

The derivatives of 4-(1H)-quinazolinone **138** are formed with yields of 58-63% when the amidine hydrochlorides **139** are boiled with the anhydrides **140** in pyridine [79].

The reaction of α-hydroxyindole with the anhydrides **1** and **2** at 180°C in the presence of 1,2-bis(dimethylamino)ethane was studied in [84]. In the case of the anhydride **2** the reaction takes place with difficulty and leads to compound **147**, i.e., the product from condensation of equimolar amounts of the reagents (yield 32%).

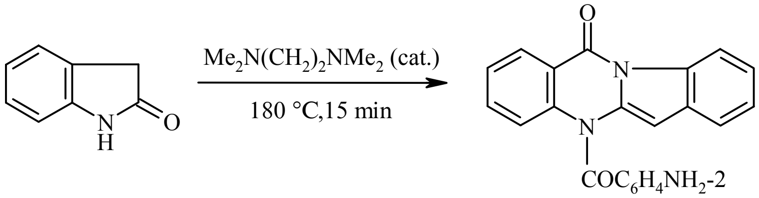
2 +



147

In the case of the anhydride **1** the product from the reaction of one mole of α-hydroxyindole with two moles of the anhydride **148** is formed [84].

1 +

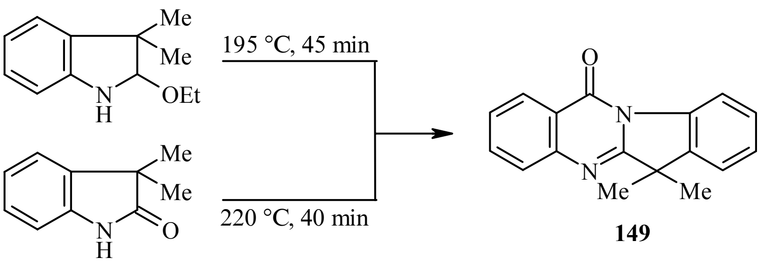


148

The product **149** with a similar structure but with the multiple bond in a different position is obtained as a result of the condensation of the anhydride **1** with 2-ethoxy-3,3-dimethylindole (yield 28%) or with 3,3-dimethyl-2-oxoindole (yield 38%) at high temperatures [85].

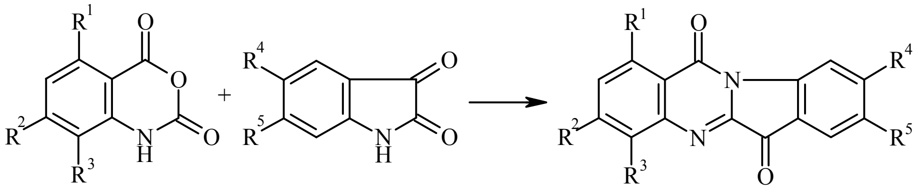
1 +

1 +



149

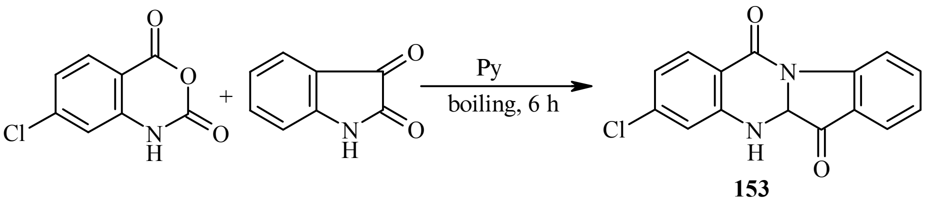
Compounds **152** were obtained in the reaction of the isatoic anhydrides **1** and **150** with isatin and its derivatives **151** in DMF in the presence of diisopropylcarbodiimide (0.5 h, 95-100°C) [87].



1, **150** **151** **152**

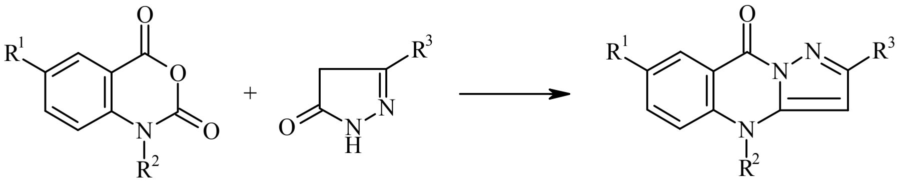
R^1, R^2, R^3, R^4, R^5, (yield, %): H, H, H, H, H, 93 or 68 – without carbodiimide; H, H, Cl, H, H, (36); Cl, H, H, H, H, (63); Cl, H, Cl, H, H, (29); H, H, Br, H, H, (35); H, H, O_2N, H, H, (26); H, O_2N, H, H, H, (9); Cl, H, H, H, O_2N, (52); Br, H, H, H, O_2N, (31) [86]; H, H, H, H, H, (68); Br, H, H, H, H, (82); H, H, H, Cl, Cl, (76); Br, H, H, H, Br, (84) [87]

An analog of compounds **152** — the indoloquinazoline derivative **153** — was obtained with a 23% yield by boiling 7-chloroisatoic anhydride with isatin in pyridine [88].



153

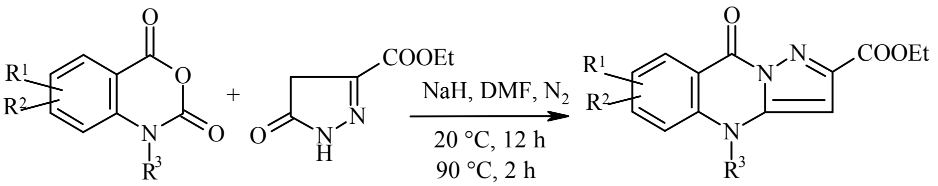
The pyrazoloquinazolines **154** were synthesized from the anhydrides **60** and 3-R^3-Δ^2-pyrazolin-5-ones by the action of sodium hydride in DMF (20°C, 15 h, 90°C, 1 h) [89], by heating in xylene (140°C, 6 h) [90], or by heating in water (75°C, 10 h) [91]



60 **154**

R^1, R^2, R^3, (yield, %): Cl, Me, Me, (25); H, Me, EtOCO, (19); Cl, Me, EtOCO, (46); F, Me, EtOCO (26); Cl, $PhCH_2$, EtOCO (2); Cl, Et, EtOCO (20); MeO, Me, EtOCO (15, at 20 °C, 72 h and at 90 °C, 3 h) [89]; H, H, Ph, (85) [90]; H, H, Me (67) [91]

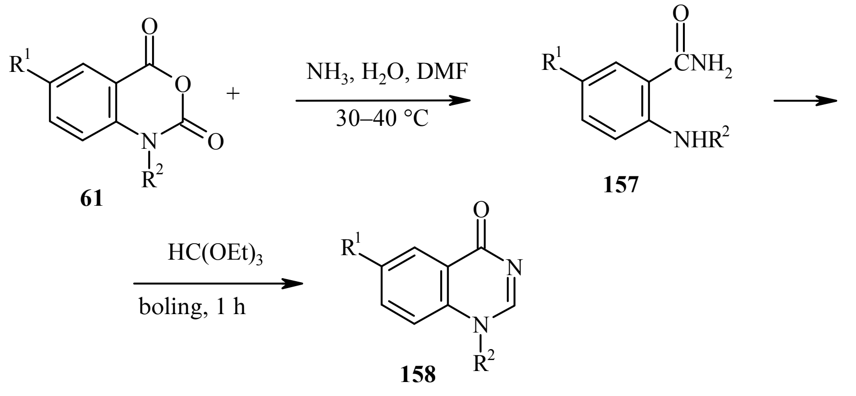
A series of pyrazoloquinazolones **155** (yields 5-99%) were also obtained by the condensation of the anhydrides **156** with 3-ethoxycarbonyl-Δ^2-pyrazolin-5-one in DMF in an inert gas atmosphere in the presence of sodium hydride [92].



156 **155**

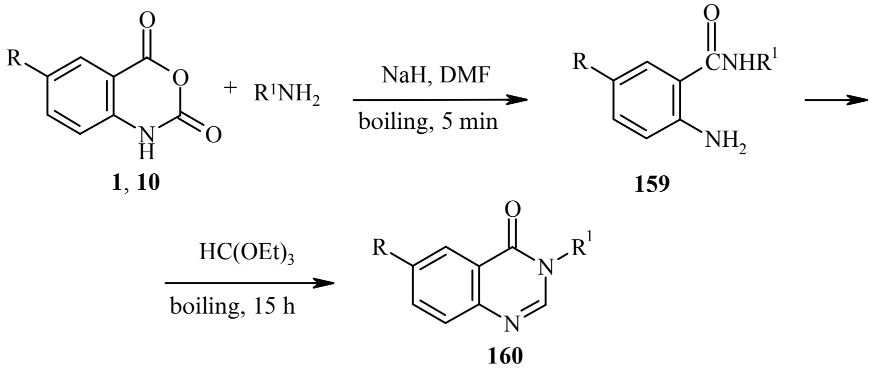
R^1 = 7-Cl, 7-F, 7-Me, 7-MeO, 7-NH_2, 7-MeCONH, 7-PrO, 5-MeO, 8-MeO, 5-Me, 7-HO, 5-HO, 8-F_3C, 7-HOOC, 6-HOOC; R^2 = H, 6-MeO, 6-Cl; R^3 = Me, Et, Pr

As stated above, the synthesis of quinazoline derivatives can also be conducted in two stages, i.e., by the reaction of isatoic anhydrides with ammonia, amides, and various compounds containing the NH_2 group followed by cyclization of the obtained anthranilic acid derivatives. Thus, the amino amides **157**, formed during the action of aqueous ammonia on the anhydrides **61** (yields 61-73%), were brought into reaction with orthoformic ester, and this led to the quinazolinones **158** (yields 53-78%) [79].



R^1, R^2 = H, MeCO; H, EtOCO; Br, MeOCO; Cl, MeOCO; H, $NCCH_2$

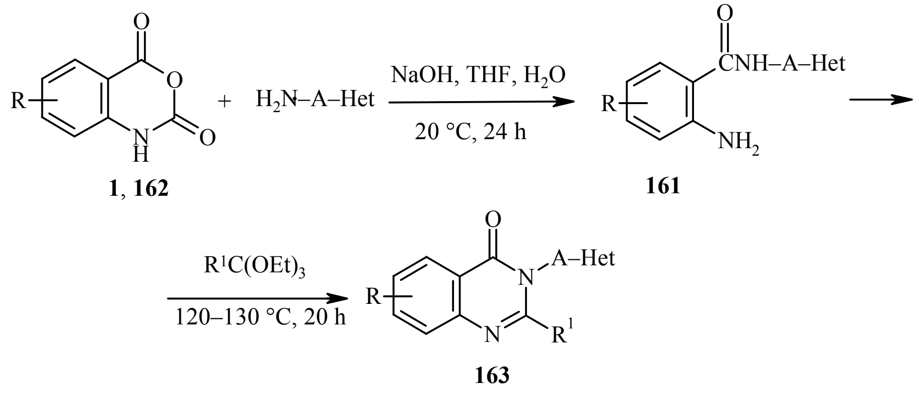
The amino amides **159**, obtained from the anhydrides **1** and **10** and primary amines, were converted into derivatives of 4-quinazolinone **160** with high yields by boiling with orthoformic ester [93-95].



R, R^1NH_2: H, 9,10-dihydrolysergamine [93]; H, 5-aminotetrazole [94]; Br, anthranilic acid [95]

If oxaloacetic anhydride was used instead of the orthoester in the production of quinazolone **160** (R^1 = H, R^2 = 5-tetrazolyl) (80°C, 40 min; 20°C, 3 h), the yield of the product was reduced to 67% [94].

The derivatives of anthranilic acid **161**, formed as a result of the reaction of the anhydrides **1** and **161** with amines containing an imidazolyl residue, were converted into compounds **163** by condensation with orthoesters [96].



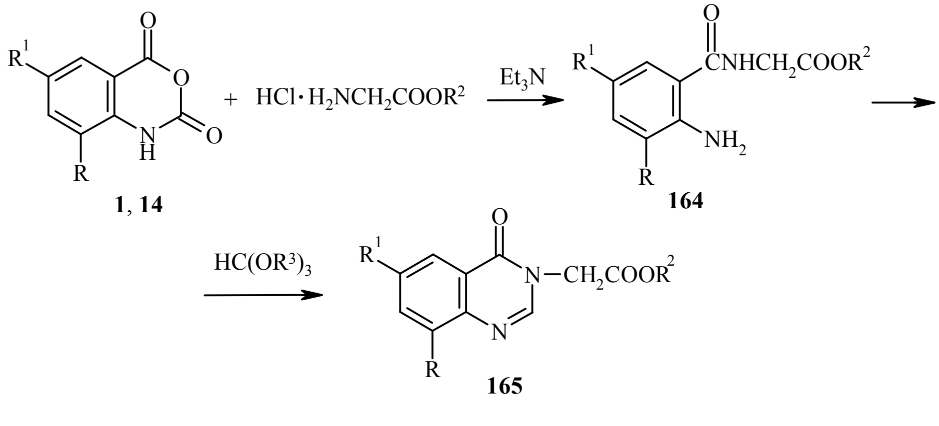
R = H, 6-Cl, 7-Cl, 6-Me; R^1 = Me, Et; A = $(CH_2)_n$ (*n* = 3-8, 10), $CH_2CH(Me)CH_2$, CH_2CH_2CHMe; Het = 1-imidazolyl

The derivatives of anthranilic acid **161** were obtained from the anhydrides **1** and **162** and amides containing a hetraryl residue at a higher temperature, and they were converted more rapidly into the derivatives of 4-quinazolinone [97].

1, **162** + H_2NCO–A–Het $\xrightarrow[\text{90 °C, 45 min}]{\text{PhMe}}$ **161** $\xrightarrow[\text{100–120 °C, 2 h}]{HC(OEt)_3}$ **163**

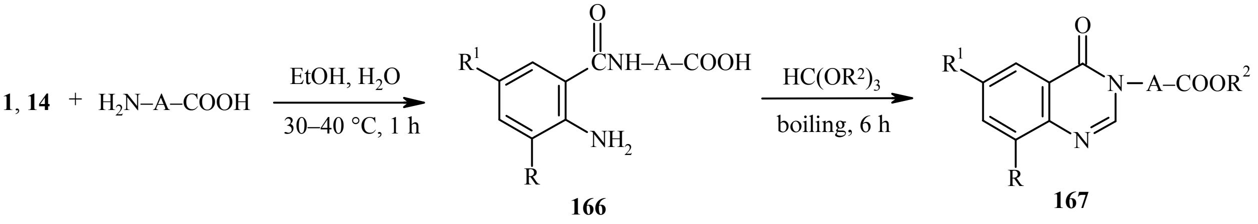
R = H, 6-Cl, 6-Br, 6-Me; R^1 = H; A = $(CH_2)_n$ (*n* = 3, 4, 8), $CH_2CH(Me)CH_2$, CH_2CH_2CHMe;
Het = 1-imidazolyl, 2-phenyl-1-imidazolyl, 1,2,4-triazol-1-yl, 3-pyridyl

The anhydrides **1** and **14** react with glycine and its esters in alcohol (60-70°C, 10 min) [75] and in water (35-40°C) [98] in the presence of triethylamine and are converted into the anthranilic acid derivatives **164**. The latter undergo cyclization at the second stage of the reaction with orthoesters $HC(OR^4)_3$ (140–150 °C [75]; 100 °C [98]) to the products **165** (yields 42-93%).



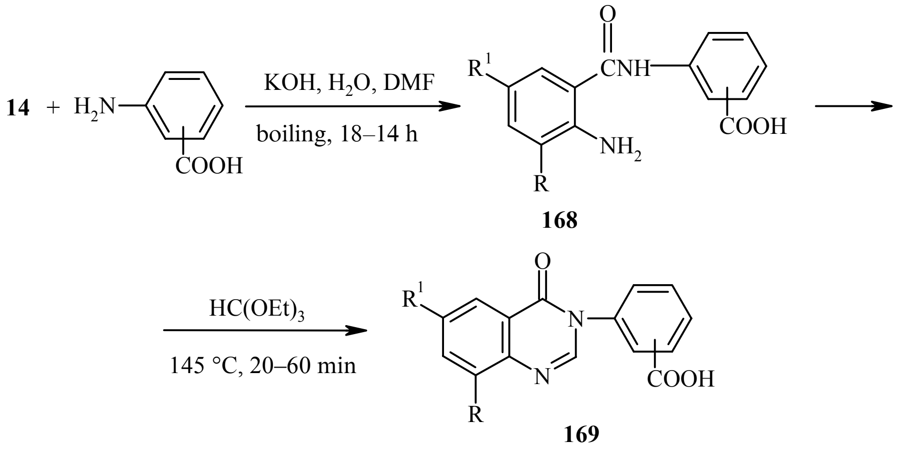
R, R^1, R^2 = H, Cl, Me; Br, Br, Me; Cl, Cl, Me [75]; H, H, H; H, Cl, Et; Cl, Cl, H;
H, H, Et; Br, Me, H; H, Br, H; H, Cl, H; Br, Br, H [98]; R^3 = Me, Et

In the case of compounds **166**, which are the products from the reaction of the anhydrides **1** or **14** and amino acids, not only cyclization but also esterification with the formation of esters **167** (yields 24-73%) occurs at the second stage [99].



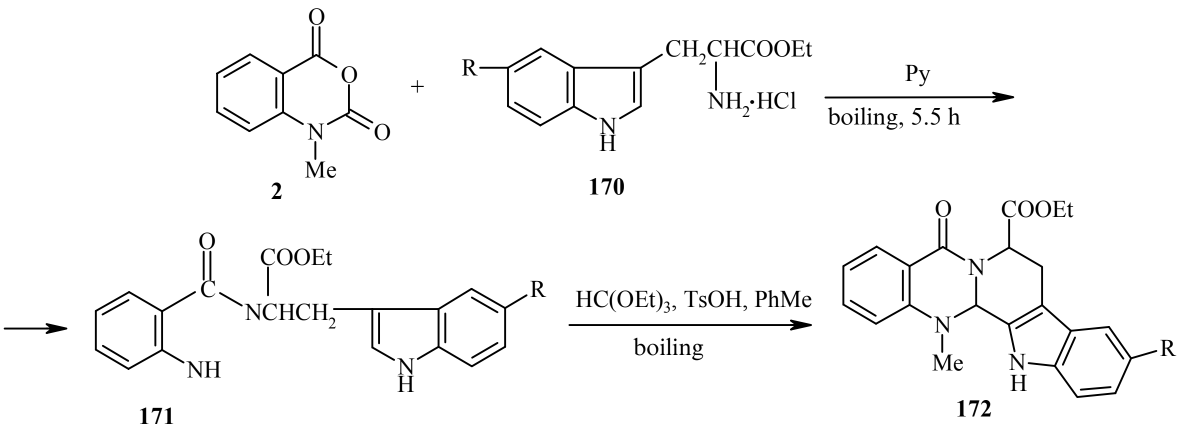
R, R[1], R[2], A = H, H, Et, CH₂; H, Br, Me, CH₂; H, Cl, Et, CH₂; H, H, Me, CH₂=C;
H, H, Et, MeCH; Br, Br, Et, MeCH

The amino amides **168** are formed from the anhydrides **14** and *ortho*- or *para*-aminobenzoic acid under harsher conditions than with the aliphatic amino acids. At the second stage of this process aromatic acids **169** with a quinazolonyl substituent are formed from compounds **168** [100].



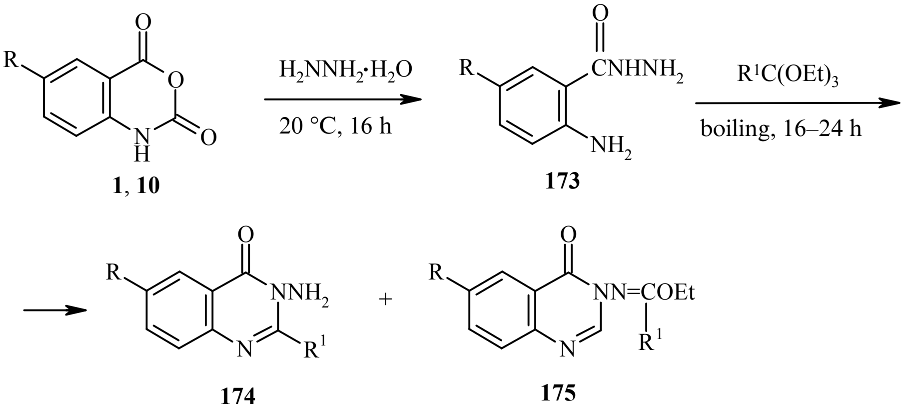
R = H, Cl, Br; R[1] = H, Cl, Br

The reactions of the anhydride **2** and the hydrochlorides of α-amino-β-indolyl- or α-amino-β-(5-methoxyindolyl)propionic acid **170** give high yields (97 and 88%) of the corresponding amides **171**. When heated with orthoformic ester in the presence of TsOH the latter undergo cyclization to the condensed pentacyclic compounds **172** (yields 66 and 69% respectively) [101].



R = H, OMe

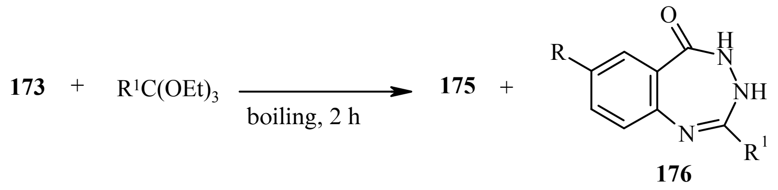
Interesting results were obtained during investigation of the reaction of the isatoic anhydrides **1** and **10** with hydrazine followed by cyclization of the obtained hydrazides by the action of orthoesters. Thus, the anhydride **10** (R = NO_2) and hydrazine hydrate gave the corresponding hydrazide **173** (yield 88%). When boiled with an excess of orthoacetic ester the product gave two compounds, i.e., the aminoquinazolinone **174** (R^1 = Me, yield 44%) and the iminoquinazolinone **175** (R^1 = Me), which is the product from the reaction of the amino derivative with the orthoester (yield 2%) [10



R = H, Cl, Br, O_2N; R^1 = H, Me

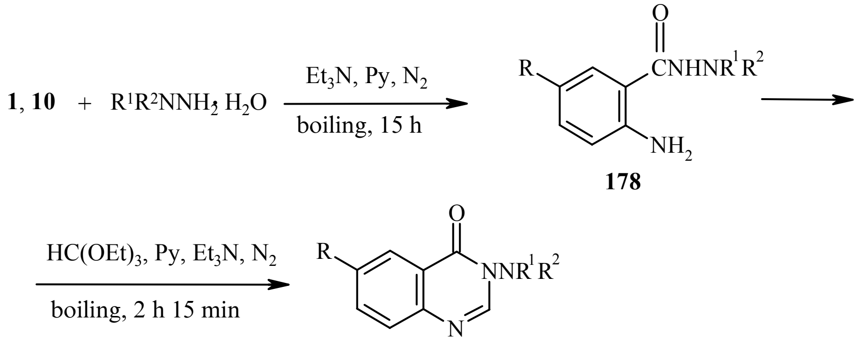
The formation of compounds **174** and **175** is determined by the structure of the employed orthoester and by the conditions under which the process is conducted. Thus, only the products **174** (yields 60-81%) were obtained when the hydrazides **173** (R = H, Cl, Br, NO_2) were boiled with orthoformic ester (R^1 = H) in alcohol for 24 h [13]. In the same paper compounds **175** were obtained with yields of 17-98% when the hydrazides **173** (R = H, Me, Et) were boiled for not less than 20 h with an excess of orthoformic, orthoacetic, or orthopropionic esters (R = H, Me, Et). The identities of R and R^1 and the reaction times (h) were as follows: H, H. 20; H, Me, 40; H, Et, 48; Me, H, 120: Me, Me, 48; Me, Et, 192; Et, H, 264; Et, Me, 168; Et, Et, 48; H, Me, 72).

Only the product **174** (R = Br, R^1 = Me) (yield 69%) was obtained from the hydrazide (**173**) (R = Br) and orthoacetic ester (EtOH, 20 °C, 33 days) [13]. The same authors [13] report that mixtures of the corresponding imino derivative **175** and 1,3,4-triazepin-5-one **176** were formed when the hydrazides (**173**) (R = H, Br) were boiled with orthoformic, orthoacetic, or orthopropionic ester without a solvent.



R, R^1, (yield **175** and **176**, %): H, H, (57 and 16); Cl, Et, (40 and 13); Br, Me, (27 and 25)

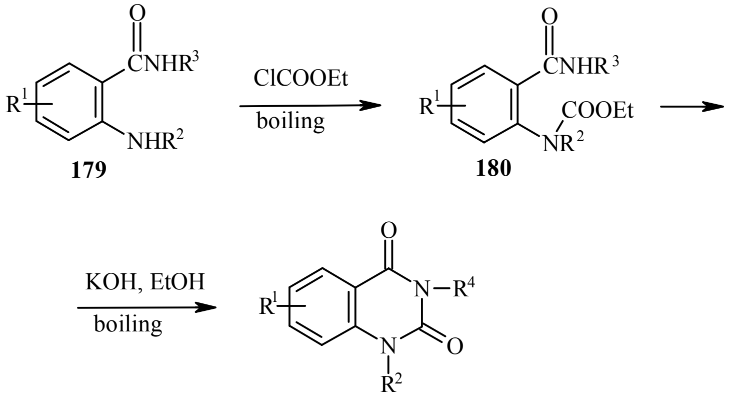
The aminoquinazolinones **177** were synthesized with yields of 26-71% by heating the hydrazides [formed from the anhydrides **1** or **10** and the hydrochlorides of disubstituted hydrazines] with orthoformic ester in the presence of triethylamine and pyridine in an atmosphere of nitrogen [103]



178, **177**

R, R[1], R[2]: H, H, *t*-Bu; H, $-(CH_2)_2O(CH_2)_2-$; H, H, Ph; Cl, $-(CH_2)_5-$; Cl, $-(CH_2)_2O(CH_2)_2-$; Cl, H, $PhCH_2$

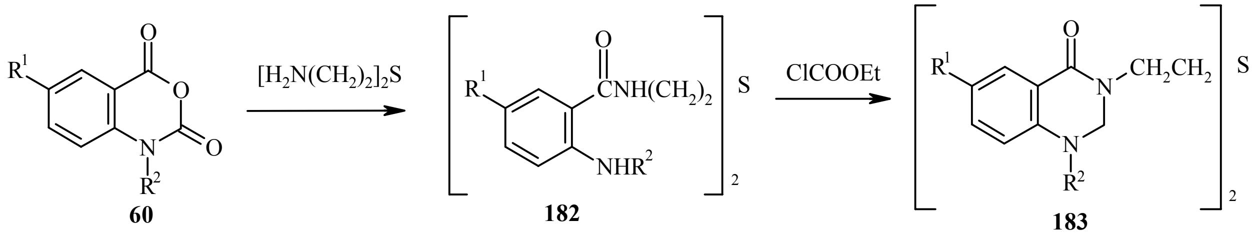
The derivatives of anthranilic acid **179** (the products from the condensation of primary amines and the respective isatoic anhydrides) were treated with orthocarbonic ester, and the obtained compounds **180** were cyclized to the derivatives of 2,4-quinazolinedione **181** by the action of an alcohol solution of potassium hydroxide [67, 96, 104, 105].



179, **180**, **181**

For **179** and **180** R[1], R[2], R[3] = H, $HOOCCH_2$, $MeOOCCH_2$; 5-Cl, $HOOCCH_2$, $MeOOCCH_2$; H, Me, $MeOOCCH_2$ [67]; (H, 5-Cl, 4-Cl, 3-Cl, 5-Br, 5-Me or 3-F_3C), H, imidazol-1-yl-A [A = $(CH_2)_n$ (n = 3–8, 10), $CH_2CH(Me)CH_2$ or CH_2CH_2CHMe] [96]; H, H, 1-benzyl-4-piperidinyl; 5-Cl, H, 1-benzyl-4-piperidinyl [104]; 3,5-Br_2, H, $MeOOCCH_2$ [105]. For **181** R[1], R[2], R[4] = H, $HOOCCH_2$, $HOOCCH_2$; 6-Cl, $HOOCCH_2$, $HOOCCH_2$; H, Me, $HOOCCH_2$ [67]; (H, 6-Cl, 7-Cl, 8-Cl, 6-Br, 6-Me or 8-F_3C), H, imidazol-1-yl-A [A = $(CH_2)_n$ (n = 3–8, 10), $CH_2CH(Me)CH_2$ or CH_2CH_2CHMe] [96]; H, H, 1-benzyl-4-piperidinyl; 6-Cl, H, 1-benzyl-4-piperidinyl [104[; 6,8-Br_2, H, $HOOCCH_2$ [105]

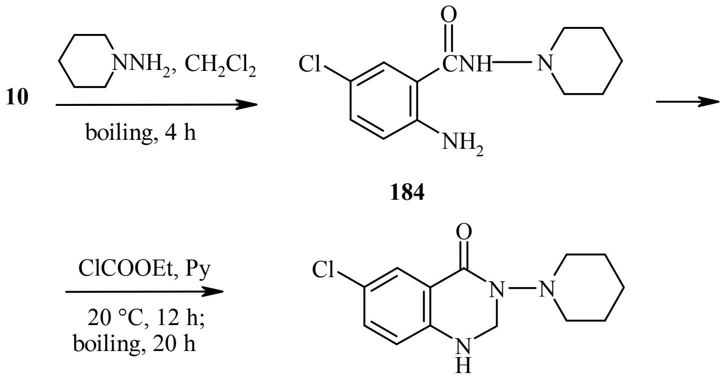
The reaction of the anhydrides **60** with bis(2-aminoethyl) sulfide gave the sulfides **182**, which were converted by the action of carbonic ester into compounds **183** [106, 107].



60, **182**, **183**

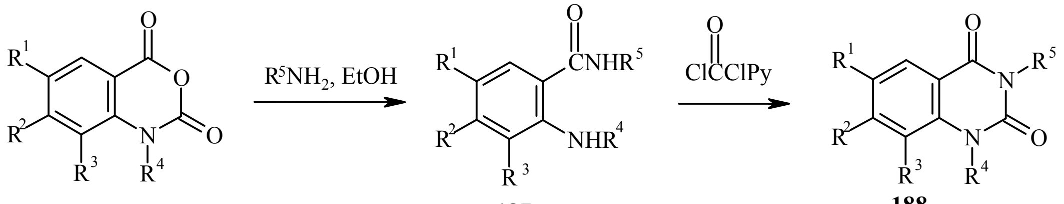
R[1] = H, F, Cl, Br, I, Me, MeO; R[2] = H, alkyl, $PhCH_2$, Ph

The anthranilic acid derivative **184**, formed with a 74% yield from 6-chloroisatoic anhydride **10** and 1-aminopiperidine, is converted with a 38% yield into 6-chloro-3-(1-piperidinyl)quinazoline-2,4(1H,3H)-dione (**185**) when treated with ethyl chlorocarbonate [108]



185

The anhydrides **186** react with primary amines in alcohol and form compounds **187**. The reaction of the latter with phosgene in pyridine (80°C) [104], in boiling benzene [109, 110], or in toluene (90°C) [111] leads to cyclization with the formation of 2,4-quinazolinedione derivatives **188** [104, 109-111].

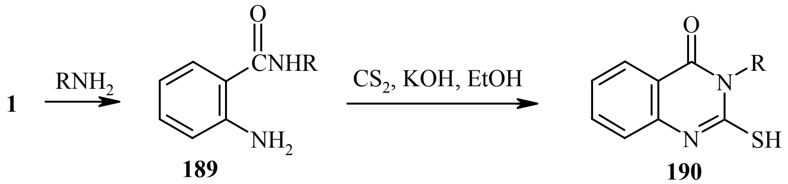


186 **187** **188**

R^1 = H, Cl, MeO, Br; R^2 = H, Cl, MeO; R^3 = H, Cl; R^4 = H, Me, Et, $CH_2{=}CHCH_2$, $PhCH_2$, 4-Br-2-$FC_6H_3CH_2$; R^5 = Me_2N, Et_2N, 4-morpholyl, 1-piperidinyl, 4-methyl-1-piperazinyl, MeONH, $MeOCOC_6H_4NH$, $MeOCOCH_2$, *t*-$BuOCOCH_2$, 3,4-$Cl_2C_6H_3$

The reaction of some of the above-mentioned anhydrides **187** (R^1 = Cl, Br; R^2 = R^3 = H; R^4 = *t*-$BuOCOCH_2$, 2-F-4-$BrC_6H_3CH_2$; R^5 = $MeOCOCH_2$, 3,4-$Cl_2C_6H_3CH_2$) with thiophosgene in toluene or dioxane at 80-100°C resulted in the formation of 1-R^4-3-R^5-6-R^1-quinazoline-2-thioxo-4-ones [111].

The reaction of the anhydride **1** with amines in dioxane (20°C, 2 h) [112], alcohol (boiling, 2 h) [113], or benzene (boiling, 10 h) [114] gave 63-83% yields of anthranilic acid derivatives **189**, which were converted by the action of hydrogen sulfide in the presence of potassium hydroxide into 2-mercapto-4-quinazolinones **190** (yields 40-92%) [112-114].

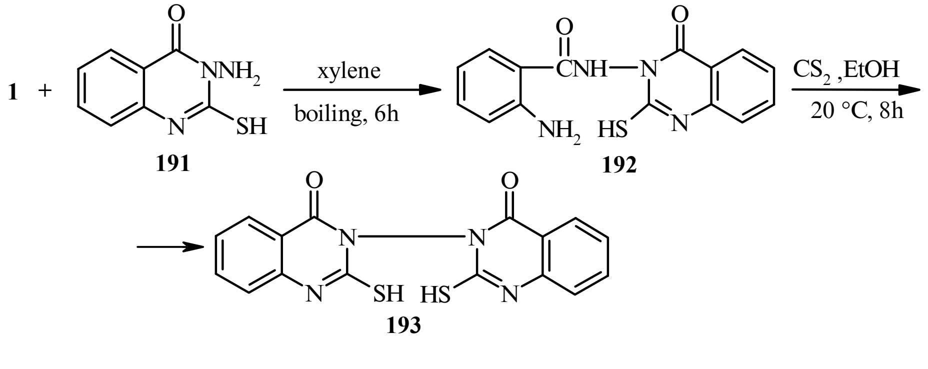


189 **190**

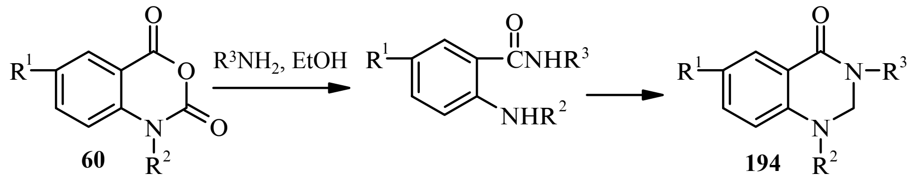
R = $EtO(CH_2)_2$ [112]; NH_2, PhNH, EtOCONH [113]; AcNH, PhNH [114]

Compound **190** (R = PhNH) was also obtained by treatment of the corresponding anthranilic acid derivative **189** with hydrogen chloride in ether (2.25 h), with potassium isothiocyanate in aqueous alcohol (20°C, 12 h), and treatment of the reaction mixture at 110-112°C for 1.5 h [114].

The reaction of the anhydride **1** with 3-amino-2-mercaptoquinazolin-4(3H)-one (**191**) gave a 76% yield of the anthranilic acid derivative **192**, which was converted by the action of hydrogen sulfide in alcohol into 3,3-bis(2-mercapto-4(3H)-quinazolinone) (**193**) with a yield of 85% [115].

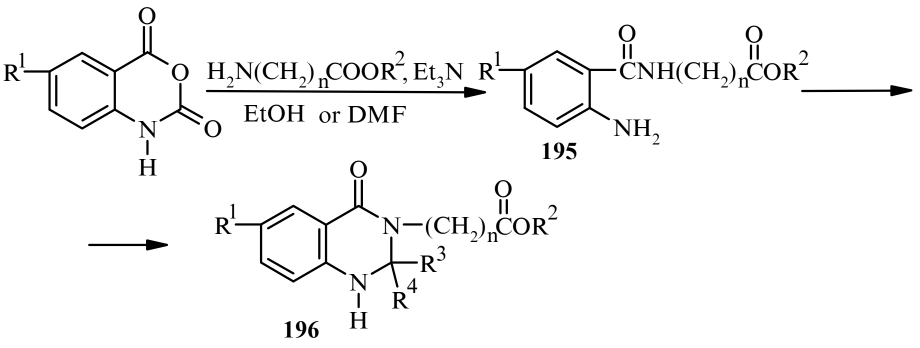


The derivatives of 1,2-dihydro-4(3H)-quinazoline-one **194** are formed when the products from the reaction of the anhydrides **60** with amines are heated with formaldehyde. The cyclocondensation of compounds **194** takes place when they are boiled with an alcohol solution of hydrogen chloride (3 h) [116] or heated in anhydrous dioxane or toluene (80-100°C) [111].



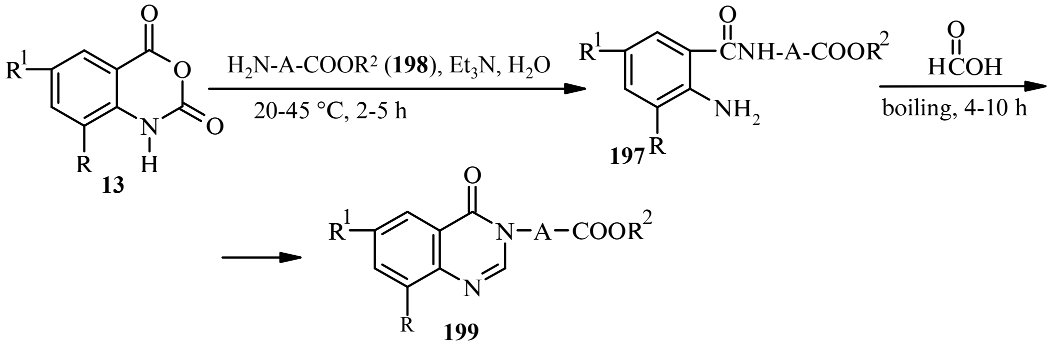
R^1, R^2, R^3 : Br, 4-Br-2-$FC_6H_3CH_2$, $MeOCOCH_2$; Cl, *t*-$BuOCOCH_2$, 3,4-$Cl_2C_6H_3CH_2$ [111];
H, $EtOCOCH_2$, 4-$MeOC_6H_4CH_2$ (yield 81%) [116]

The amino amides **195** were obtained from isatoic or 6-iodoisatoic anhydrides and the esters of amino acids. They were converted by the action of aromatic aldehydes or acetone into derivatives of dihydro-4-quinazolone **196** (ethanol, piperidine, boiling for 1 h, or conc. hydrochloric acid, boiling for 6 h [117]; toluene, toluenesulfonic acid, boiling for 0.5 h, [118]).



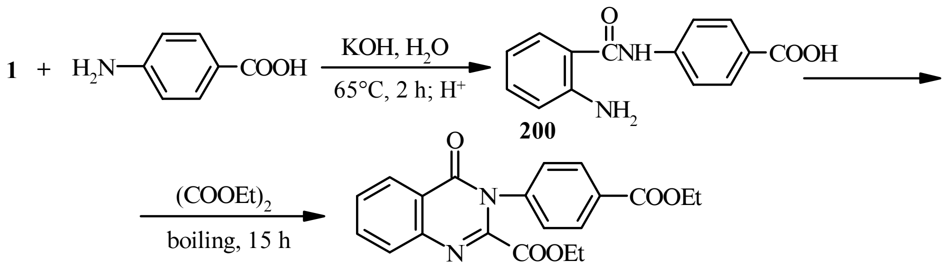
R^1, R^2, R^3, R^4, *n*, (yield of **196**, %): H, Me, H, Ph, 1, (75); H, Me, Me, Me, 1, (15) [117];
I, Et, H, 4-ClC_6H_4, 2, (–) [118]

Compounds **197** – the products of the reaction of the anhydrides **13** with the amino derivatives **198** – are converted by boiling in formic acid into acids or esters **199** with a 4-quinazolinone residue (yields 24-93%) [119, 120].

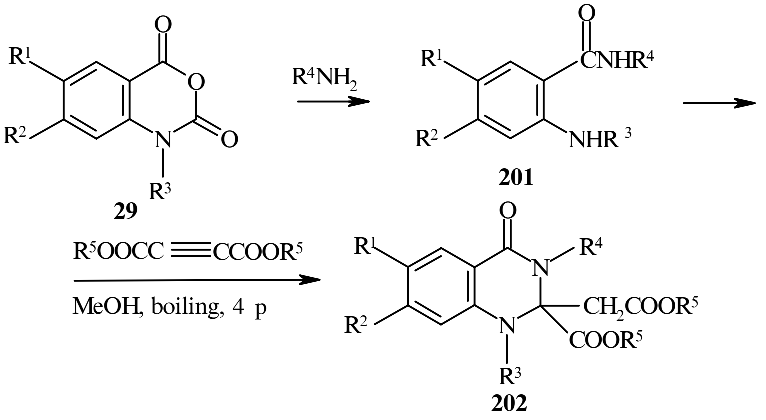


R = H, Cl, Br; R^1 = H, Cl, Br; R^2 = H, Me, Et; A = CH_2, $(CH_2)_2$, $(CH_2)_3$, MeCH, CH_2=C, $CH_2CH(OH)CH_2$ [119];
R^1 = R^2 = R^3 = H; A = $CH_2CONHCH_2CONHCH_2$ [120]

The action of diethyl oxalate on the amide **120** obtained from the anhydride **1** and *p*-aminobenzoic acid gave a 23% yield of 2-ethoxycarbonyl-3-(4-ethoxycarbonylphenyl)quinazoline-4(3H)-one [100].

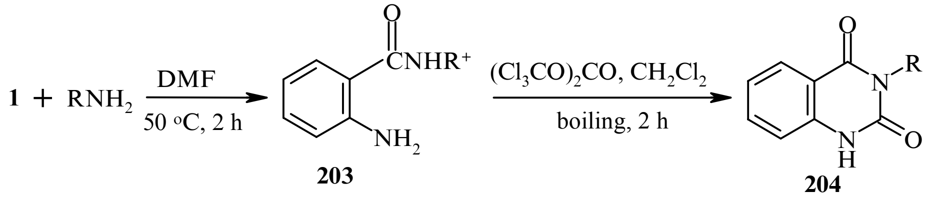


The diesters **202** were synthesized in a similar way from the amino amides **201**, obtained from the anhydrides **29** with primary amines, by treatment with acetylenedicarboxylic esters [121, 122].



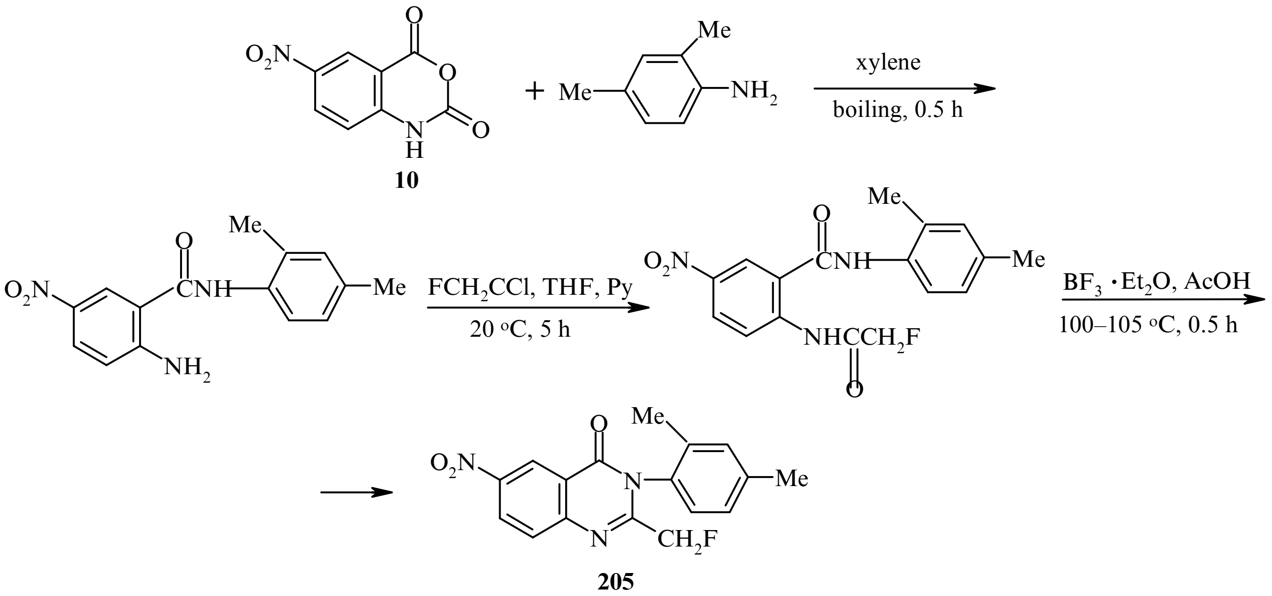
R^1 = H, Cl, OMe; R^2 = H, MeO; R^1R^2 = –OCH_2O–; R^3 = Me; R^4 = CH_2, $HOCH_2$;
R^5 = Me (yield 40–91%) [121]; R^1 = H, Cl; R^2 = R^3 = H;
R^4 = 2-ClC_6H_4, 4-ClC_6H_4, *t*-BuCO, MeO; R^5 = Me, Et [122]

The derivatives of anthranilic acid **203** [from the anhydride **1** and primary amines yields 60-88%] were converted by the action of thiophosgene into 3-R-quinazoline-2,4(1H,3H)-diones **204** (yields 78-88%) [123].

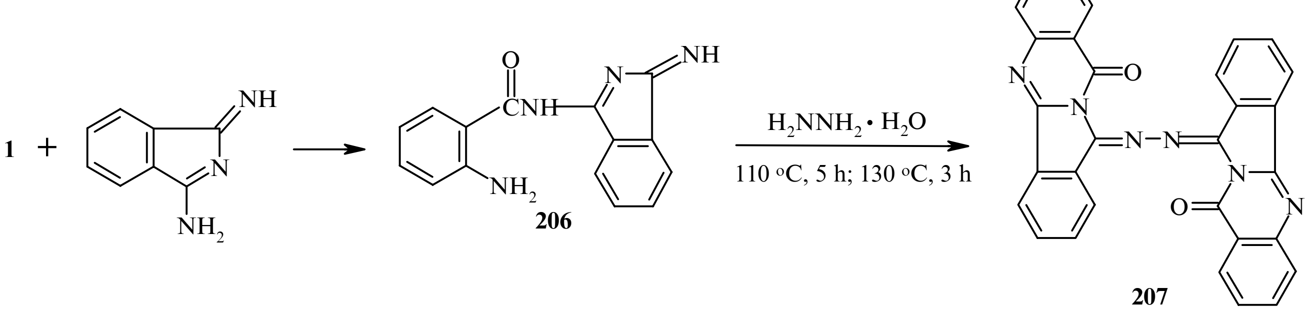


R = Ph, PhCH(Me), $Ph(CH_2)_2$, 3-$MeOC_6H_4$, (4-phenyl-1-piperazinyl)ethyl

The three-stage synthesis of compound **205** (yield 70%), in which boron trifluoride etherate was used at the cyclocondensation stage, has been patented [124]. The yields at the first and second stages amounted to 82 and 93% respectively.

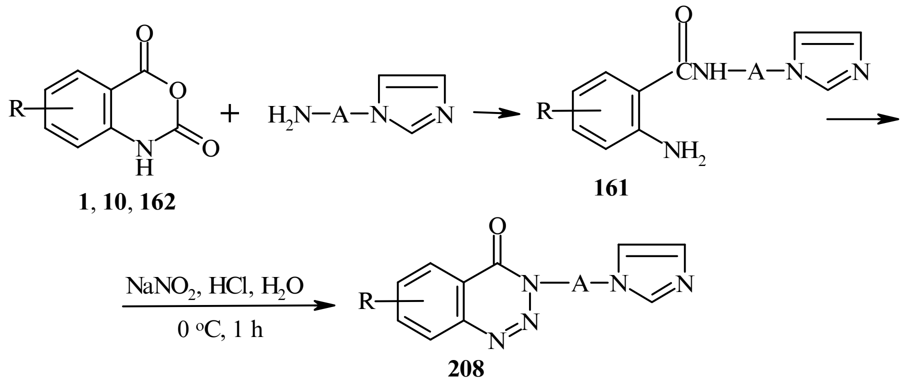


The anthranilic acid derivative **206** (from anhydride **1** and 1-amino-3-iminoindolenine) was converted into compound **207** when heated with hydrazine hydrate [125].



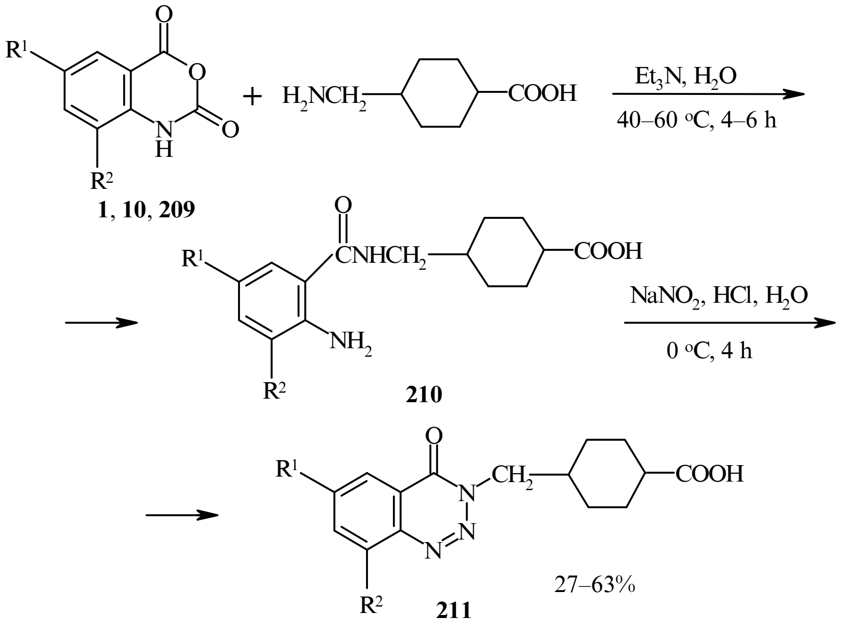
2.3. Reactions Leading to the Formation of Six-membered Rings with Three Nitrogen Atoms

The construction of six-membered rings with three nitrogen atoms on the basis of isatoic anhydrides has only been described for 1,2,3-benzotriazines. This method for the synthesis of the latter includes reaction of the anhydrides with primary amines and subsequent diazotization of the obtained amino amides, which dictates the use of initial isatoic anhydrides not containing substituents at the nitrogen atom. Thus, the action of sodium nitrite and hydrochloric acid on the amino amides **161**, formed from the anhydrides **1**, **10**, **162** and imidazolylalkylamines, leads to diazotization and cyclization with the formation of derivatives **208** of benzo-1,2,3-triazin-4-ones (yields 36-85%) [96, 126].



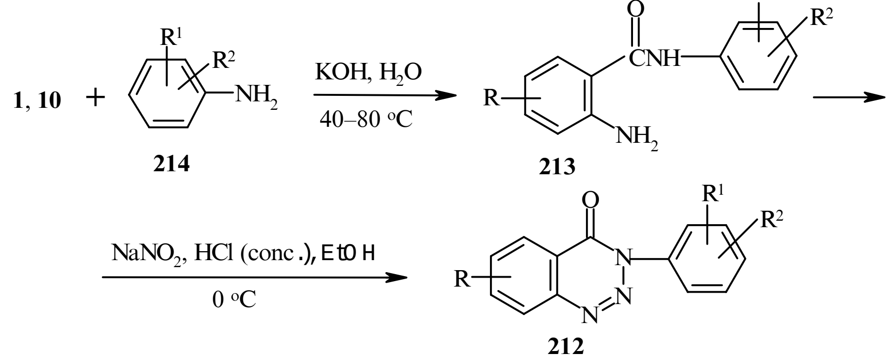
R = H, 6-Cl, 7-Cl, 6-Br, 6-Me; A = $(CH_2)_n$ (*n* = 3-6, 8), $CH_2CH(Me)CH_2$

The reaction of the anhydrides **1**, **10**, **209** with *trans*-4-(aminomethyl)cyclohexanecarboxylic acid results in the formation of compounds **210** with yields of 38-65%. The latter are converted under the conditions of diazotization into 1,2,3-benzotriazin-4(3H)-ones **211** [127].



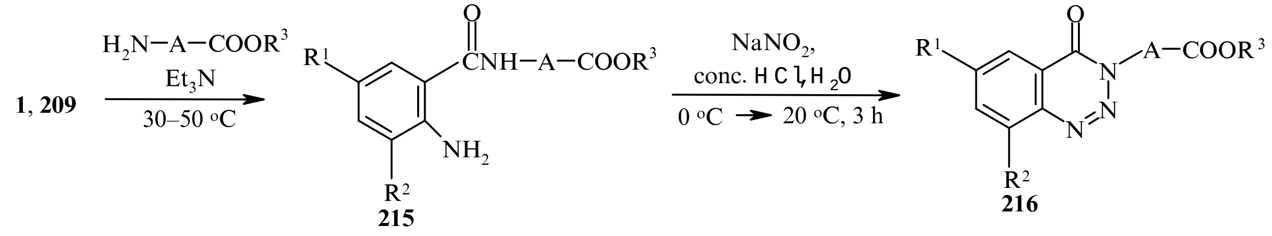
R^1, R^2 = H, H; Cl, H; Br, Br

3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-ylbenzoic acids **212** were synthesized by diazotization of the amino amides **213**, obtained by the condensation of the anhydrides **1** and **10** with aminobenzoic acids (**214**) [128].



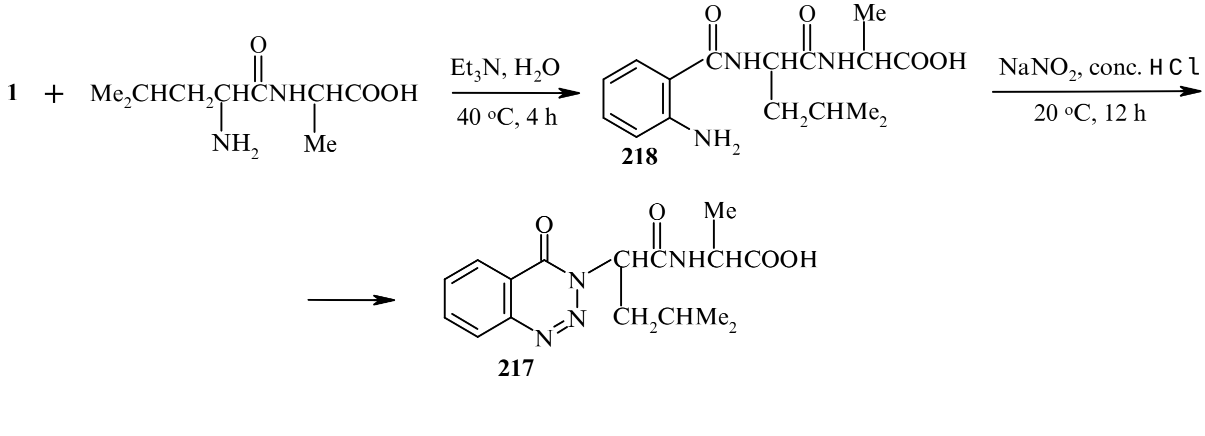
R, R^1, R^2, (yield, %): H, H, 2-COOH (58); H, H, 4-COOH, (37); 4(6)-Cl, 5-Cl, 2-COOH, (70)

In the presence of triethylamine anhydrides **1** and **209** react with aminoalkanecarboxylic esters in water or methanol, forming amino amides **215**. The latter are transformed under the diazotization conditions into derivatives of 1,2,3-benzotriazin-4-one **216** with yields of 20-90% [99, 129, 130].



R^1 = H, Cl, Br; R^2 = H, Cl, Br; R^3 = H, Me; A = $(CH_2)_n$ (n = 1–3), MeCH, Me_2CHCH, Me_2CHCH_2CH, $PhCH_2CH$, $HOCH_2CH$, *i*-PrCH, *i*-BuCH, $CH_2CH(Me)CH_2$; $ACOOR^3$ = $HOOC(CH_2)_2$, $H_2NCO(CH_2)_2$

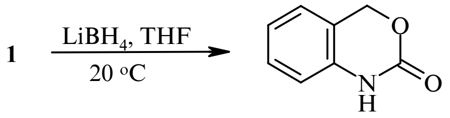
Compound **217** was synthesized with a 23% yield by the condensation of anhydride **1** with *D*,*L*-leucyl-*D*,*L*-alanine followed by diazotization of the obtained dipeptide (**218**) and cyclization [131].



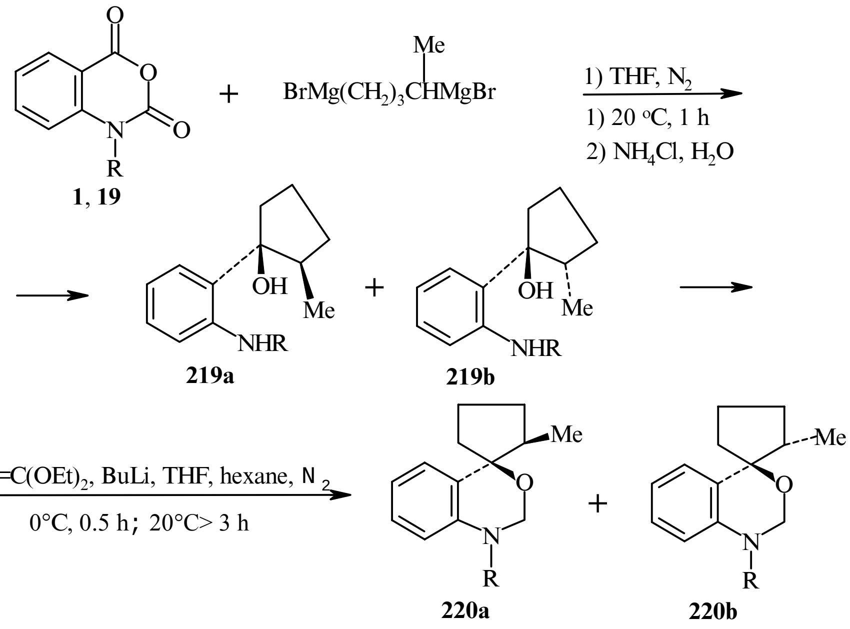
2.4. Reactions Leading to the Formation of Six-membered Rings with Two Different Heteroatoms

2.4.1. Formation of six-membered rings with nitrogen and oxygen or sulfur atoms. Almost all the papers on the transformations of isatoic anhydrides leading to the formation of new six-membered rings with two different heteroatoms have been devoted to the synthesis of derivatives of 3,1-benzoxazine. There is only one paper in which the production of a derivative of 3,1-benzothiazine is described.

Lithium borohydride reduces the carbonyl group at position 4 in anhydride **1**, and 4H-3,1-benzoxazin-2(1H)-one is formed with a yield of 73% [132].

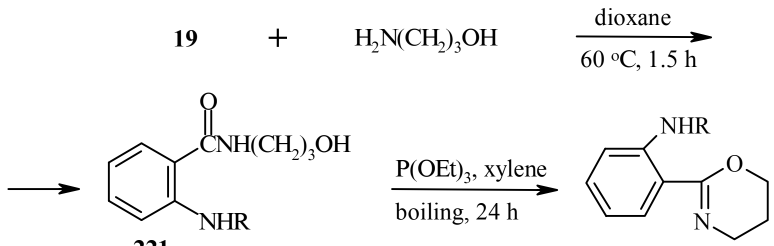


Anhydrides **1** and **19** react with the Grignard reagent BrMg(CH_2)$_3$CH(Me)MgBr to form a mixture of diastereomeric alcohols **219a**,**b** (yields 20-67%), which are converted by treatment with butyllithium and diethyl carbonate into mixtures of diastereomeric spiro compounds **220a**,**b** [133].



R,ratios **219a** : **219b** and **220a** : **220b** (total yield of product **220**): H, 33 : 67 and 33 : 67 (–); Me, 33 : 67 and 33 : 67, (85); Et, 35 : 65 and 33 : 67, (65); Pr, 20 : 80 and 42 : 58, (62); $PhCH_2$, 40 : 60 and 40 : 60, (51)

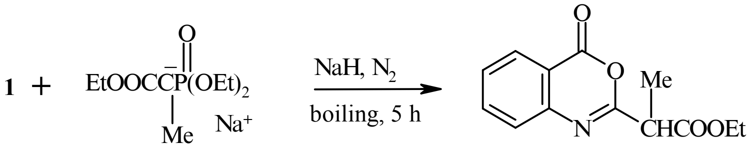
When heated with triethyl phosphite the amides of anthranilic acid **221**, synthesized (with yields of 57-83%) from the anhydrides **19** and 3-amino-1-propanol, form derivatives of dihydro-3,1-oxazine **222** (yields 24-54%) [9].



221 222

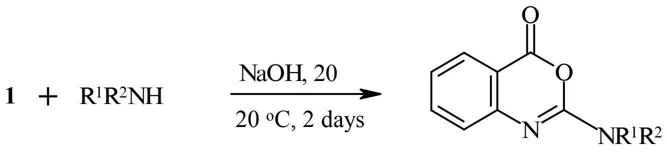
R = $(CH_2)_2O(CH_2)_2NCOCH_2$, $PhCH_2$, Ph

It has already been mentioned in part 2.1 that substituted 3,1-benzoxazin-4-ones **74** are formed together with the derivatives of benzoxazinedione **75**. We note here that the yield of compound **74** (R = Me) depends on the medium in which the reaction of the anhydride (**1**) with the sodium derivative **73** in the presence of sodium hydride is conducted; if the reaction is carried out in benzene the yield is 64%, while in a mixture of benzene and DMF the yield is 18% [47].



73 **74**

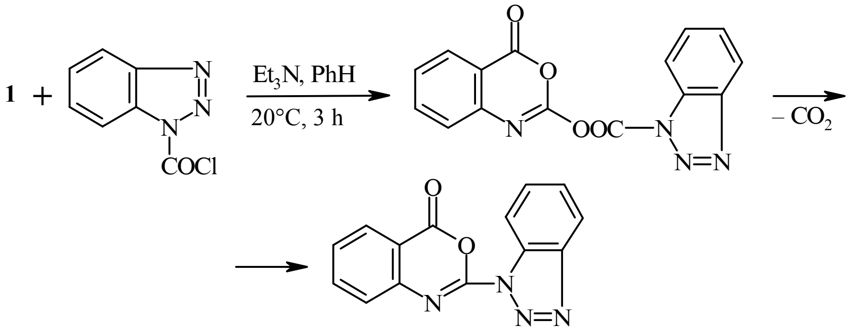
The 2-amino derivatives of 3,1-benzoxazinone **223** were obtained with yields of 12-76% from anhydride **1** and secondary amines in the presence of sodium hydroxide [134].



223

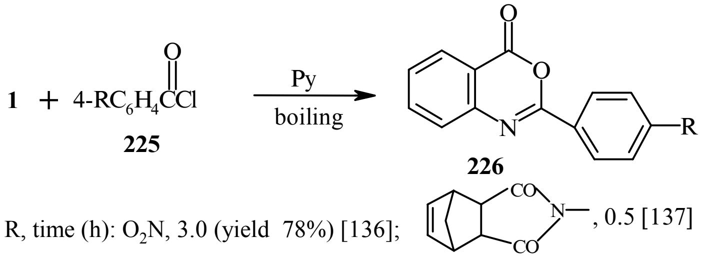
R^1, R^2 = *i*-Pr, *i*-Pr; Et, Et; Bu, Bu; *i*-Bu, *i*-Bu; $(CH_2)_4$; $(CH_2)_5$; $(CH_2)_2O(CH_2)_2$

In the reaction of the same anhydride **1** with 1,2,3-triazole-1-carbonyl chloride in the presence of triethylamine (20°C) the 3,1-benzoxazinone **224** with a benzotriazolyl substituent was obtained with an 84% yield [135].

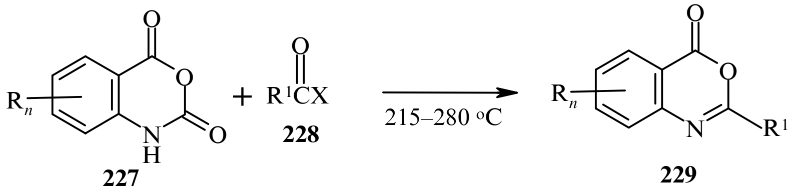


224

Anhydride **1** reacts with aromatic acid chlorides **225** in the presence of pyridine, and subsequent recyclization of the product leads to compounds **226** [136, 137].



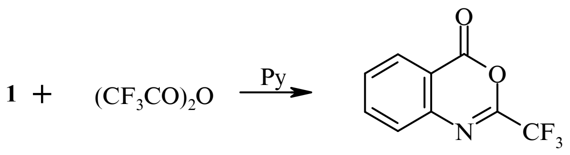
At high temperatures the isatoic anhydrides **227** react with the carboxylic acid halides **228** in the absence of bases with the formation of derivatives of 3,1-benzoxazin-4-one **229** [138].



R = Alk, HOOC, AlkO, SO_3H, O_2N, Hal; R^1 = Alk, Ar, $Ph(CH_2)_n$; n = 1, 2; X = Cl, Br

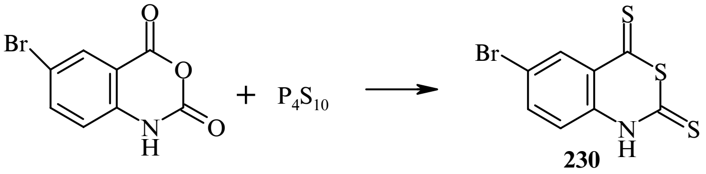
The corresponding compounds **229** (R_n = 0; R^1 = $CFCl_2CF_2$, $CF_3(CF_2)_7CH_2CH_2$, $CF_3(CF_2)_n$, n = 0, 1, 2, 6) were obtained from anhydride **1** and the chlorides of fluorine-containing carboxylic acids R^1COCl under similar conditions [139].

2-Trifluoromethyl-3,1-benzoxazin-4-one was synthesized by heating the isatoic anhydride **1** with trifluoroacetic anhydride (100°C, 5 min) [140] or by boiling these reagents (15 min) [141].

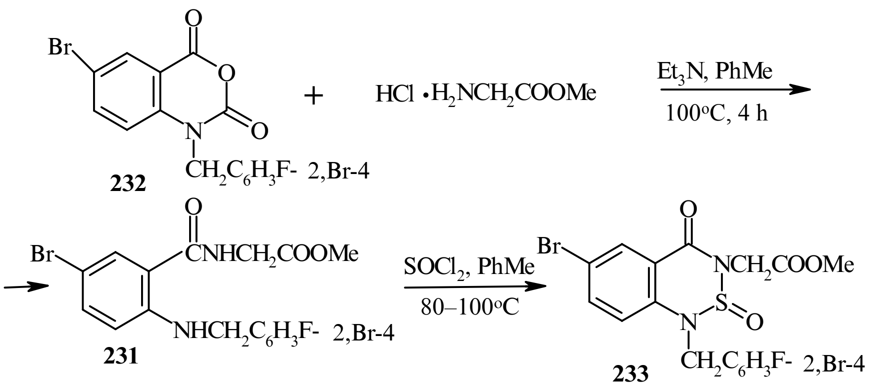


The reaction of isatoic anhydride **1** with acetic or benzoic anhydride resulted in the formation of 2-methyl-3,1-benzoxazin-4-one (yield 84%) [142] or 2-phenyl-3,1-benzoxazin-4-one [143] respectively.

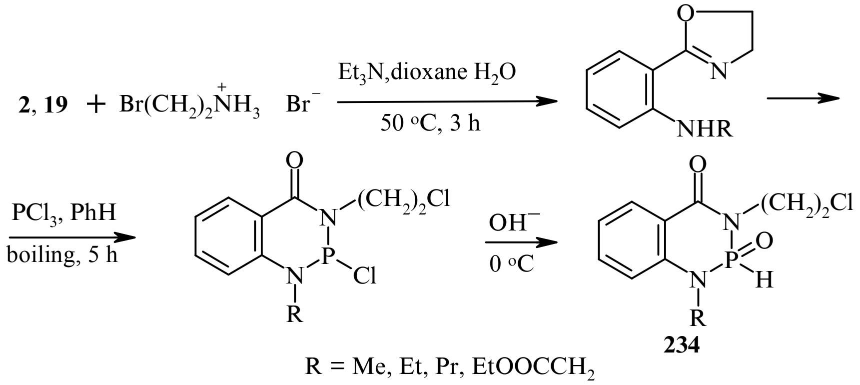
When treated with Lawesson's reagent 6-bromoisatoic anhydride is converted into 6-bromo-1H-3,1-benzothiazine-2,4-dithione **230** with a yield of 60% [144].



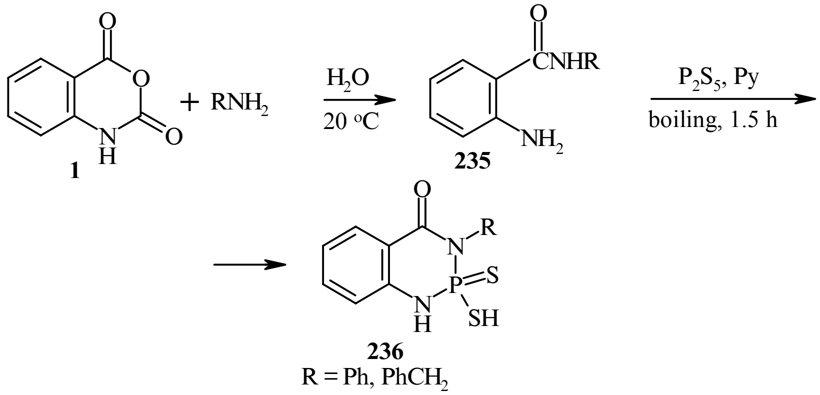
2.4.2. Formation of six-membered rings with two nitrogen atoms and a sulfur or phosphorus atom. The derivative of anthranilic acid **231**, formed with a yield of 88% as a result of the condensation of the anhydride **232** with glycine methyl ester hydrochloride, undergoes cyclization to benzothiadiazinone S-oxide **233** when heated with thionyl chloride [111].



Compounds **234**, containing two nitrogen atoms and a phosphorus atom in a six-membered ring, were obtained with yields of 60-83% from the anhydrides **2** and **19** in a three-stage synthesis [11].

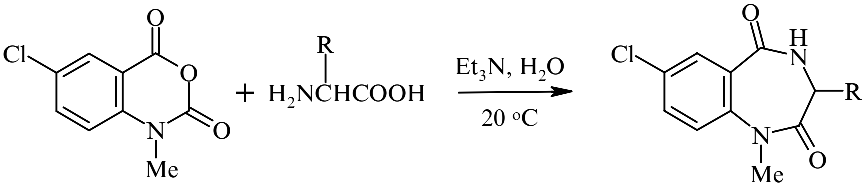


In the reaction of the anhydride **1** with primary amines the derivatives of anthranilic acid are formed with a 91% yield. When treated with P_2S_5 in pyridine the products are converted into derivatives of benzodiazaphosphorinane **236** with yields of 71 and 73% [145].



3. REACTIONS LEADING TO THE FORMATION OF SEVEN-MEMBERED RINGS WITH TWO OR THREE NITROGEN ATOMS

Aminoacetic acid and α-aminopropionic acids react with the anhydride **85** at normal temperature in the presence of triethylamine, and derivatives of 1H-1,4-benzodiazepine-2,5-dione (**237**) are formed [146].

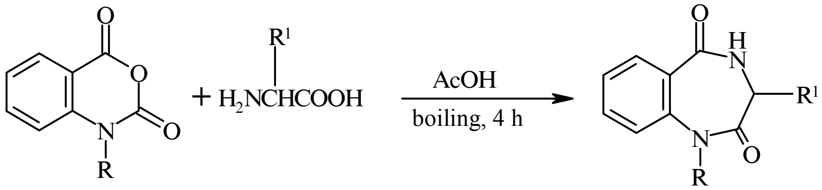


85 **237**

R, time, h (yield, %): H, 5, (92); Me, 18, (44)

If sodium carbonate is used instead of triethylamine, the yield of the product **237** (R = H) is reduced to 80% [146]. In the case of 6-chloroisatoic anhydride the same reaction was carried out with additional boiling in acetic acid, and the homolog of compound **227**, not containing a methyl substituent at position 1, was obtained [146].

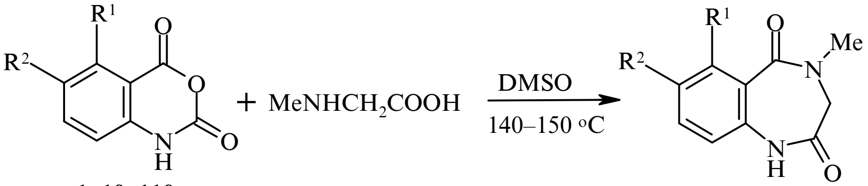
More recently it was shown in the case of the reaction of the anhydrides (**1**) or (**19**) with a series of amino acids that the analogous diones **238** substituted differently at position 3 can be synthesized by boiling the reagents in acetic acid without using triethylamine [147].



1, **19** **238**

R, R^1, (yield, %): H, H, (80); Me, H, (82); Et, H, (85); $PhCH_2$, H, (85); Ph, H, (72); H, Me, (79); Me, Me, (95); Et, Me, (92); *i*-Pr, H, (87); *i*-Bu, H, (86); H, $PhCH_2$, (90); Me, $PhCH_2$, (90)

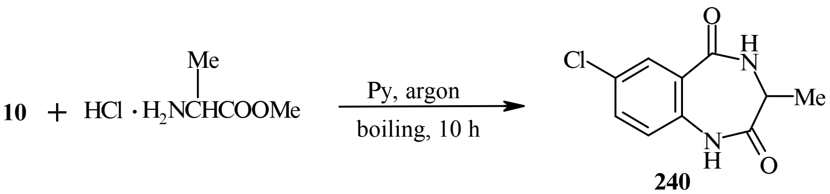
The 4-N-substituted compounds **239** were synthesized by condensation of the anhydrides **1**, **10**, **110** with N-methylaminoacetic acid (sarcosine) at 140-152°C [148-150].



1, **10**, **110** **239**

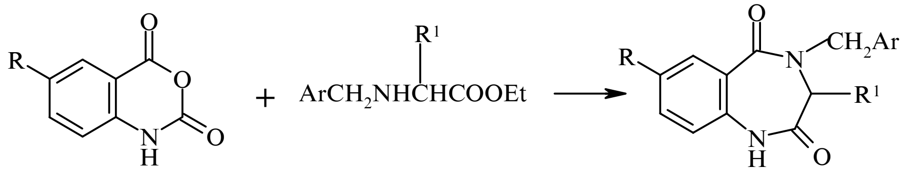
R^1, R^2 = H, H, [148]; H, Cl [148, 149]; F, H [150]; NO_2, H [151]; H, H; CF_3, H [152]

When the anhydride **10** (R = Cl) was boiled with alanine methyl ester hydrochloride in pyridine, the benzodiazepine derivative **240** was obtained (yield 52%) [153].



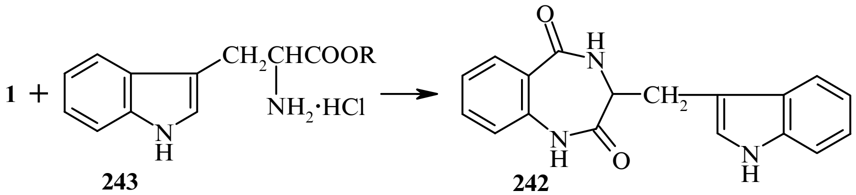
240

Compounds **241** were obtained by the condensation of the anhydrides **1** and **10** with the esters of amino acids $ArCH_2NHCH(R^1)COOEt$ (115°C, 4 h) [154] or by boiling in pyridine for 40 h [155].

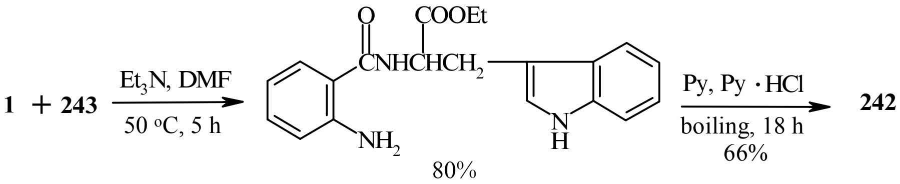


R^1, R^2, Ar, (yield, %): H, H, Ph, (30.0); Cl, H, Ph, (14.5); H, H, 2,4-$(MeO)_2C_6H_3$, (21.0) [154[;
I, 2-[(1-*t*-BuOCO (4-piperidyl)ethyl], Ph, (-) [155]

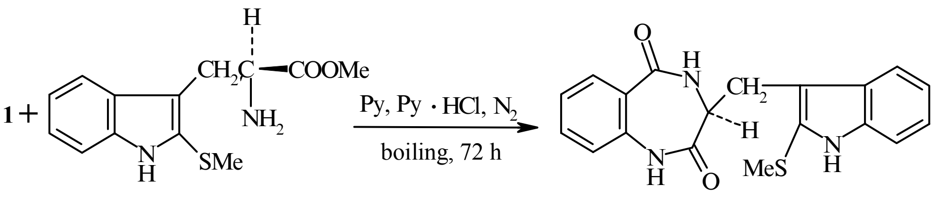
The production of derivatives of benzodiazepine **242** from the anhydride **1** and *L*-tryptophan ester **243** has been described in a series of papers. In the patent [156] it was reported that the reaction of the anhydride **1** with the amino ester hydrochloride **243** (R = Me) was conducted in the presence of triethylamine in water (16 h, 20°C). A high yield (90%) of the cyclocondensation product **242** was obtained when the reaction was carried out in two stages: 1) Treatment in water in the presence of triethylamine at 23°C for 5 h; 2) treatment in acetic acid at 118°C for 5 h [157]



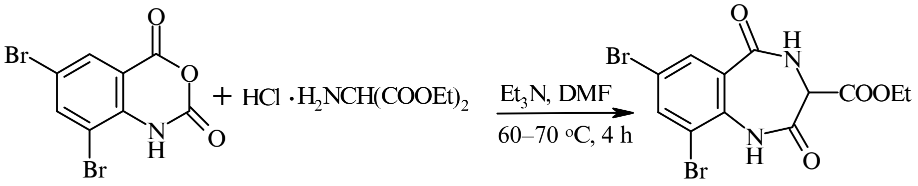
Compound **242** is also formed with an overall yield of 53% from the reaction of the anhydride **1** with the ester **243** (R = Et) when the reaction is carried out in two stages with isolation of the intermediate product [158].



The condensation of the anhydride **1** with the amino ester **244** with boiling in pyridine in the presence of pyridine hydrochloride gave a 40% yield of compound **245** [158, 159].

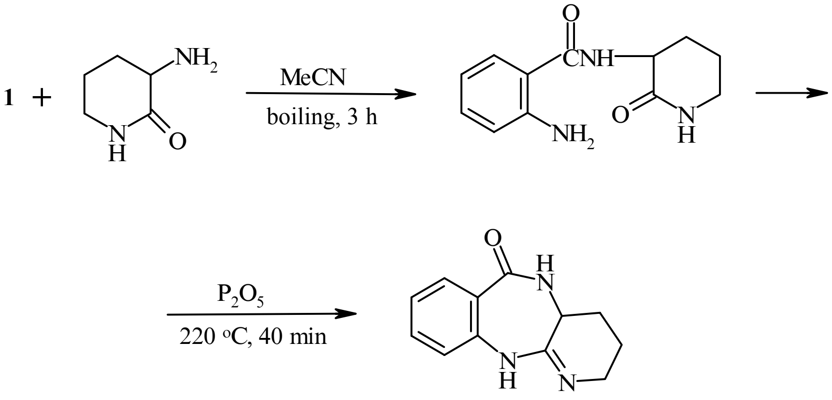


The benzodiazepine derivative **246** was synthesized (yield 49%) by heating 6,8-dibromoisatoic anhydride with diethyl aminomalonate hydrochloride in the presence of triethylamine [160].



246

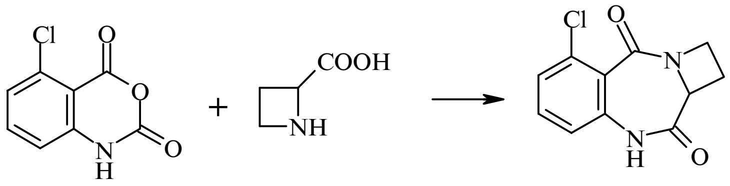
The tricyclic compound **247** was obtained with an overall yield of 80% by a two-stage synthesis: 1) Reaction of anhydride **1** with 3-amino-2-pyridone; 2) cyclocondensation of the product formed at the first stage by heating with phosphorus pentoxide [161].



247

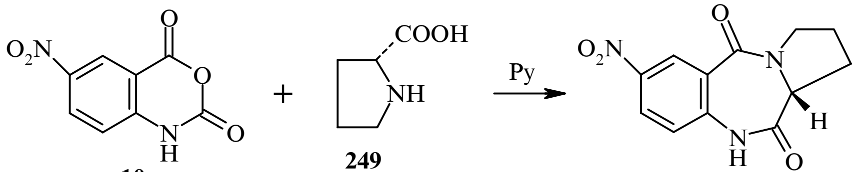
Examples of the synthesis of more complicated compounds in which a seven-membered ring in addition to a benzene ring is condensed with a four-membered or five-membered ring have been described.

A method for the production of the azetidinodiazepine derivative **248** from 5-chloroisatoic anhydride and *L*-azetidine-2-carboxylic acid has been patented [162, 163].



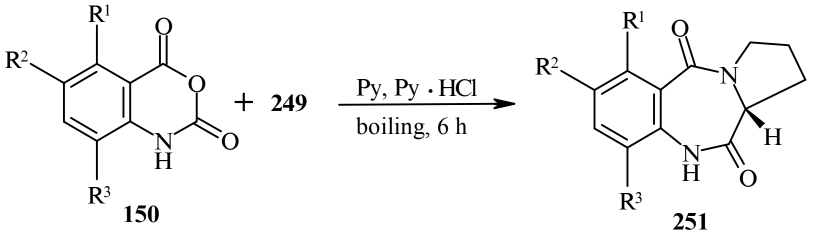
248

In the presence of pyridine 6-nitroisatoic anhydride **10** reacts with *L*-proline **249**, and 7-nitropyrrolidino[2,1-*c*]-1,4-benzodiazepine-5,11-dione **250** is formed with a 66% yield [164].



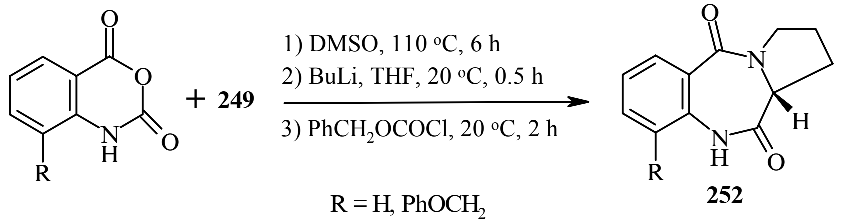
10 **249** **250**

Analogs of the latter [compounds **251**] containing methyl substituents instead of the NO_2 group at various positions in the benzene ring were obtained with yields of 73-91% by condensation of the anhydrides **150** with *L*-proline **249** in the presence of pyridine hydrochloride [165].



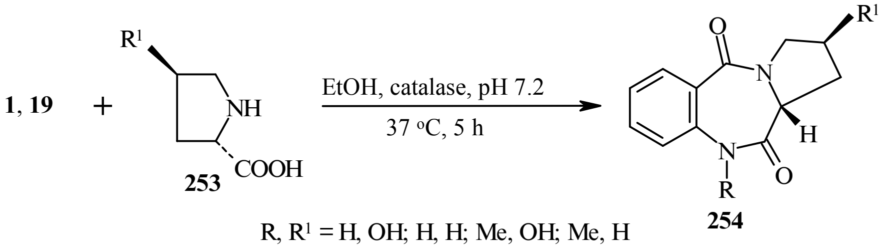
R[1], R[2], R[3]: Me, H, H; H, Me, H; H, H, Me

Compounds **252** were obtained by heating unsubstituted and 8-benzyl-substituted isatoic anhydrides with *L*-proline followed by treatment of the reaction mixture first with butyllithium or $(Me_3Si)_2NLi$, and then with benzyl chlorocarbonate [166].



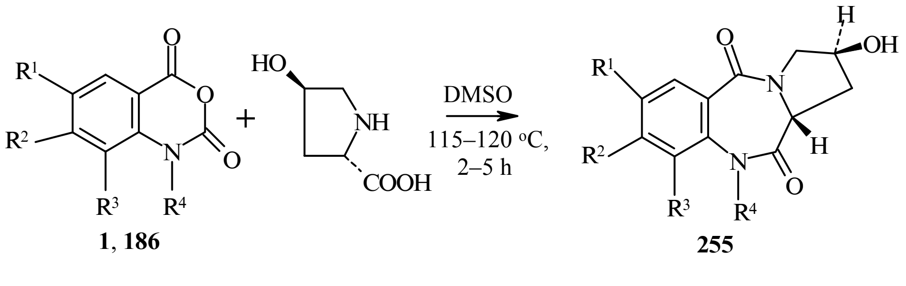
R = H, PhOCH$_2$

In the reaction of the anhydrides **1** and **19** with the amino acids **253** in the presence of catalase at pH 7.2 (phosphate buffer solution) compounds **254** were obtained with yields of 68-76% [167].



R, R[1] = H, OH; H, H; Me, OH; Me, H

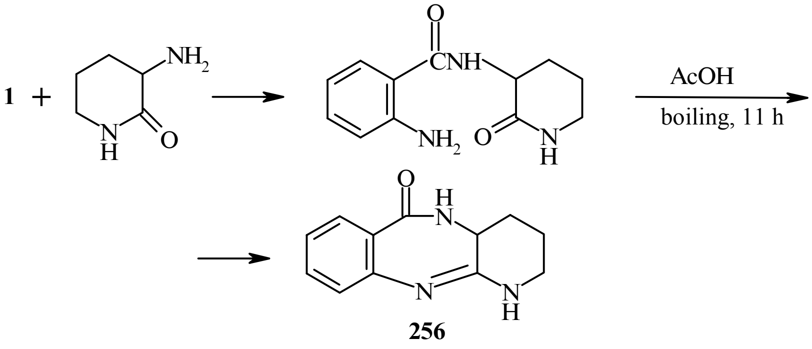
The pyrrolobenzodiazepines **255** were synthesized with yields of 58-74% by condensation of the anhydrides **1** and **186** with *trans*-4-hydroxy-*L*-proline by heating in DMSO [168-171].



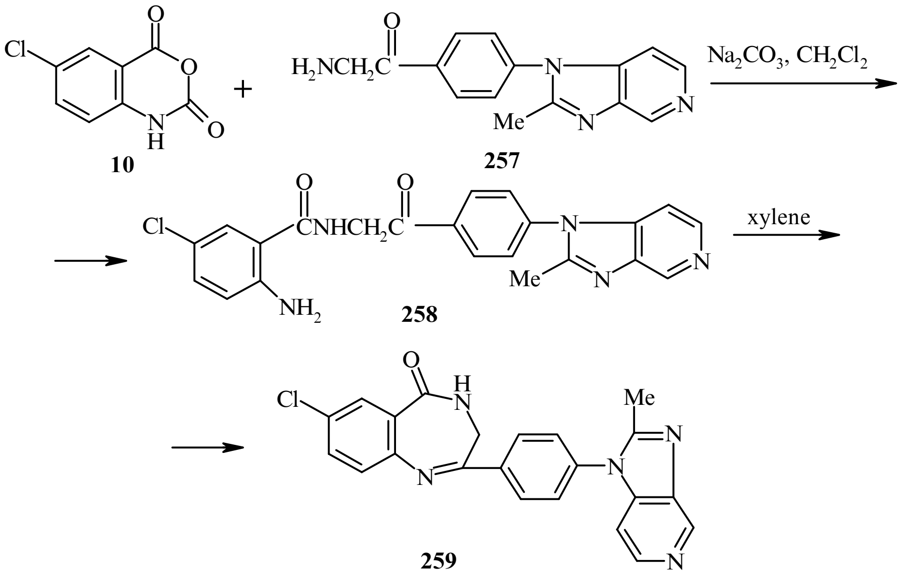
R[1], R[2], R[3], R[4] = H, Me, MeO, H, [168]; H, H, H, H; H, H, H, Me [169, 171]; Cl, H, H, H [170]

The unsubstituted product **255** (R[1] = R[2] = R[3] = R[4] = H) was obtained by the reaction of anhydride **1** with hydroxyproline in DMF at 150-155°C [172].

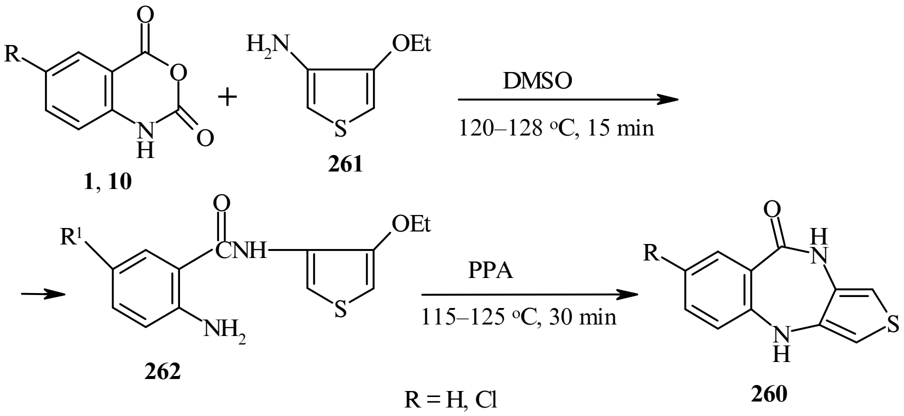
The anthranilic acid derivative formed from anhydride **1** and 3-amino-2-piperidone with a yield of 90% (see [161]) was converted into compound **256** by boiling in acetic acid [173].



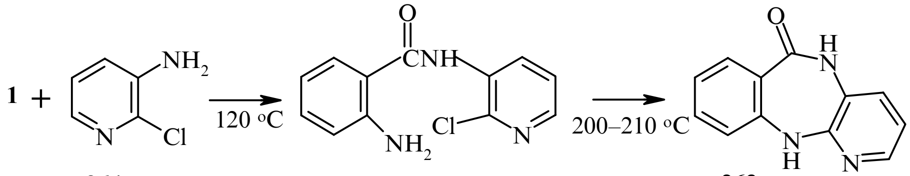
With the amino ketone **257** in the presence of sodium carbonate 6-chloroisatoic anhydride **10** forms the amino amide **258** (yield 23%), which is converted by heating in xylene into 3,4-dihydro-2-[4-(2-methylimidazo[4,5-*c*]-1-pyridyl)phenyl]-4H-1,4-benzodiazepin-5-one (**259**) with a yield of 40% [174].



7-R[1]-4H-Thieno[3,4-*b*]-1,4-benzodiazepin-9(10)-ones **260** were synthesized with yields of 73 and 88% by heating the anhydrides **1** and **10** with 3-amino-4-ethoxythiophene (**261**) followed by cyclization of the obtained compounds **262** (yields 35-59%) by heating with polyphosphoric acid [175].



A method for the synthesis of the benzodiazepine derivative (**264**) by the condensation of anhydride **1** with 3-amino-2-chloropyridine (**264**) and treatment of the obtained amino amide (**265**) at 200-210°C was filed in the patent [176].



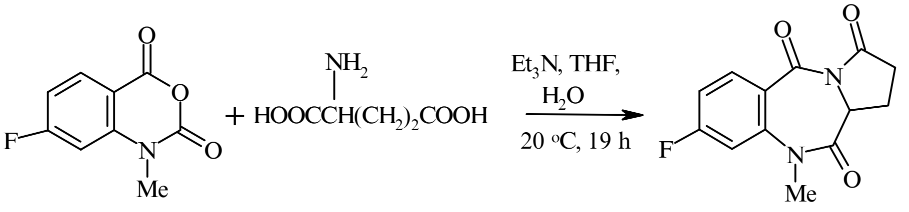
264 **265** **263**

The production of derivatives of 1,3,4-triazepin-5-one (**176**) by boiling the hydrazides (**173**) with orthoesters has already been mentioned in part 2.2.

4. REACTIONS LEADING TO THE FORMATION OF TWO NEW CONDENSED HETEROCYCLES

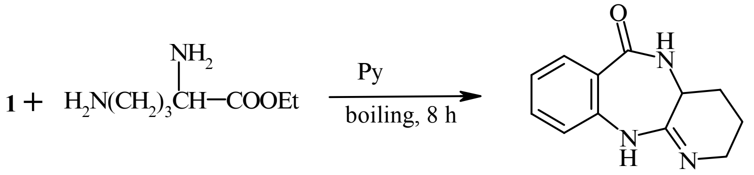
This part examines syntheses based on isatoic anhydrides in which polycyclic systems containing two new condensed heterocycles are formed in one or two stages. Some examples of the formation of such compounds are also discussed in parts 2.1, 2.2, and 3.

A derivative of pyrrolidino[2,1-*c*]-1,4-benzodiazepine **266** was synthesized by the reaction of 7-fluoro-1-methylisatoic anhydride with *L*-glutamic acid in the presence of triethylamine [177].



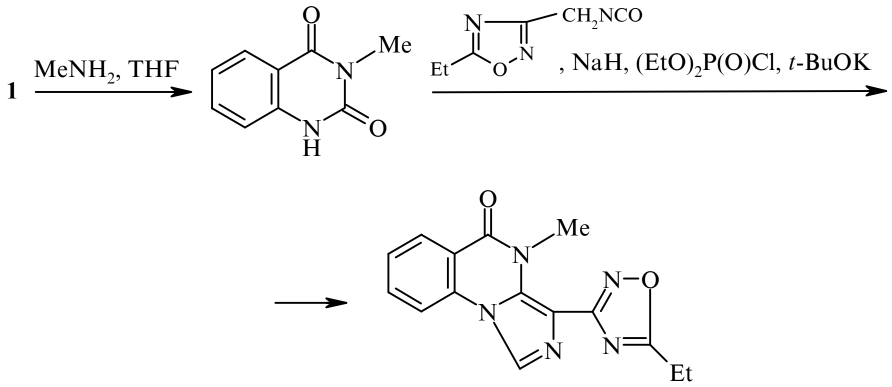
266

The production of compound **247** from the anhydride **1** and aminopyridine in two stages was described in part 3 [161]. It was reported in the same paper that the same product can also be obtained with a yield of 11% in one stage from the anhydride **1** and ornithine ethyl ester.



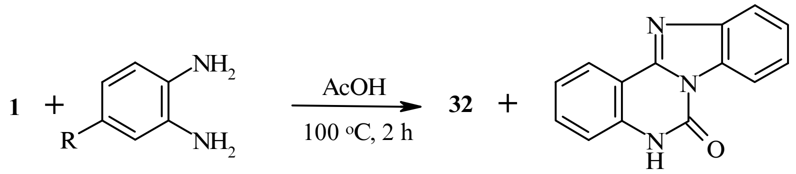
247

Compound **267**, containing condensed imidazole and quinazoline rings and also a 1,2,4-oxadiazole ring, was obtained by a two-stage synthesis [178]



267

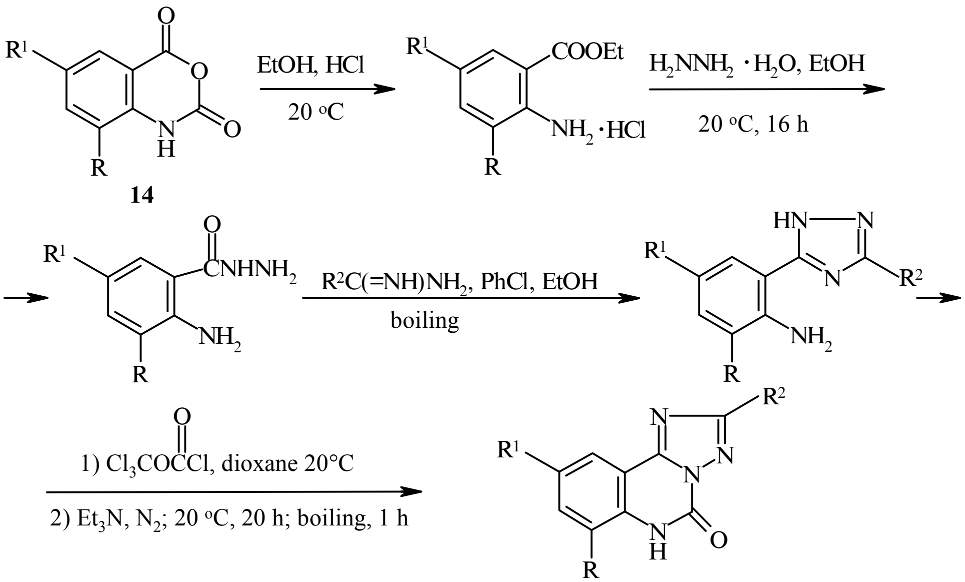
When the anhydride **1** was heated with the diamines **31** in acetic acid small yields of the benzimidazoquinazolones **268** were obtained in addition to the benzimidazole derivatives **32** (see part 1) [16].



31 **268**

R, (yield of **268, %**): H (10); Me (9); Cl (6)

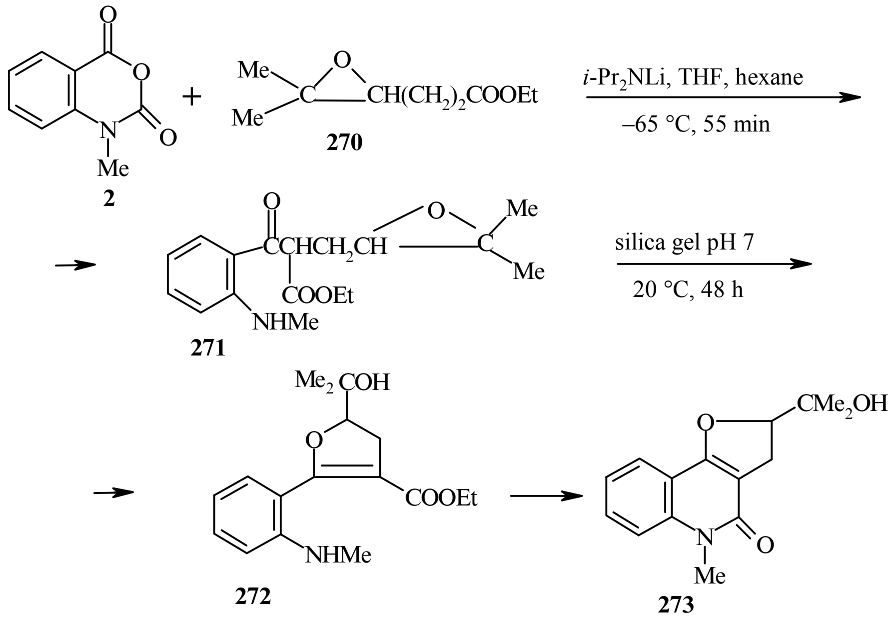
A series of 2-aryl-1,2,4-triazolo[1,5-*c*]quinazoline-5(6H)-ones **269** were obtained from the anhydrides **14** in five stages (yields 33-88%) [8].



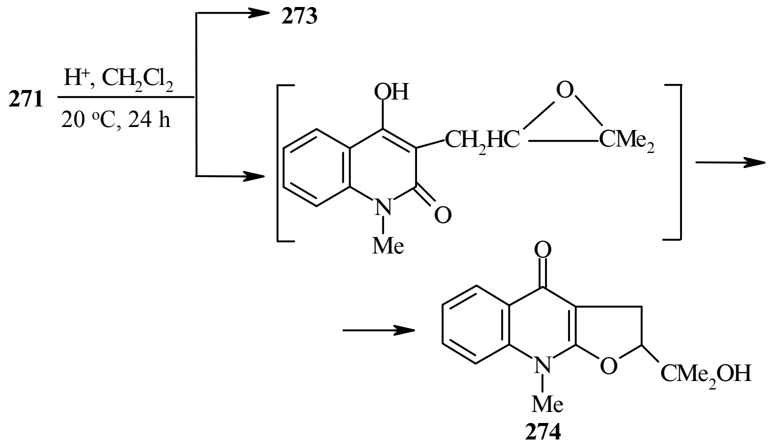
269

R, R^1, R^2, (yield, %): H, Cl, 2-pyridyl, (88); Cl, Cl, Ph, (62)

In the presence of lithium diisopropylamide the anhydride **2** reacts with the epoxide of ethyl 5-methyl-4-hexenoate **270**, forming compound **271**. The latter is converted on silica gel in a neutral medium into the dihydrofuran derivative **272**, which undergoes spontaneous cyclization to the derivative of dihydrofuroquinolinone **273** (yield 33%) [179].

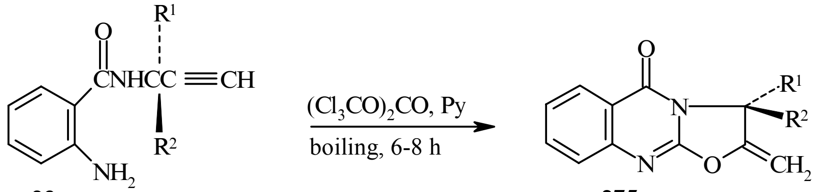


In the presence of various acids compound **271** undergoes cyclocondensation, being transformed into two isomeric furoquinolines **273** and **274** in various ratios [179].



Acid, ratio **273** : **274**: 2N HCl in CCl_4, 70 : 30; AcOH, 66 : 34;
CF_3COOH, 82 : 18; 3-ClC_6H_4COOH, 67 : 33 (yields 39 and 17%);
CF_3SO_3H, 51 : 49

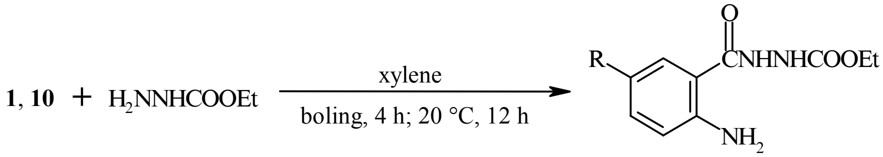
The amides **23**, i.e., the products from the reaction of the anhydride (**1**) and the acetylenic amides **21** (see part 1), undergo cyclization to the derivatives of oxazoloquinazoline **275** (yields 31-50%) when treated with triphosgene in pyridine. The configuration of the initial amines **21** and amides **23** is retained [10].



23 275

R^1, R^2 = Et, Et; $(CH_2)_5$

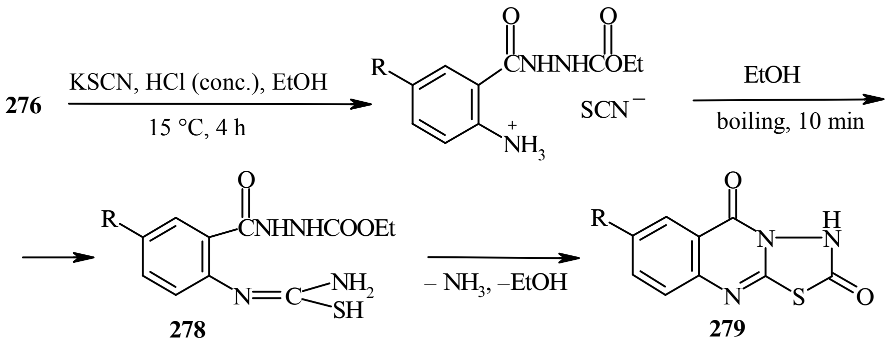
Three methods have been proposed for the synthesis of derivatives of thiadiazoloquinazolone. In all cases compounds **276**, i.e., the products of the reaction of the anhydrides **1**, **10** with ethoxycarbonylhydrazine [180], were used as starting materials.



276

R = H, Me

In the first method the amino ester **276** was treated with concentrated hydrochloric acid and KSCN in alcohol, and the obtained salt **277** (R = H) was converted by boiling in alcohol into compound **278**, which underwent spontaneous cyclization to the final product (**279**) (yield 51%) [180].



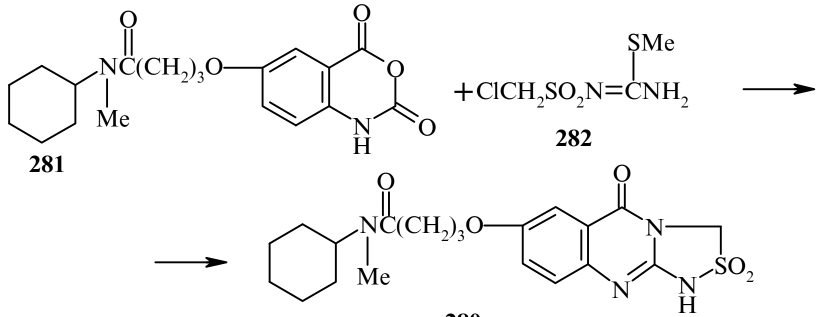
278 279

R = H

In the second method hydrogen chloride is passed through a solution of compound **276** (R = H, Me) in ether, the ether is removed, alcohol, KSCN, and water are added, and the reaction mixture is boiled for 4 h. The final products **279** (R = H, Me) are formed here with yields of 55 and 49% respectively [180].

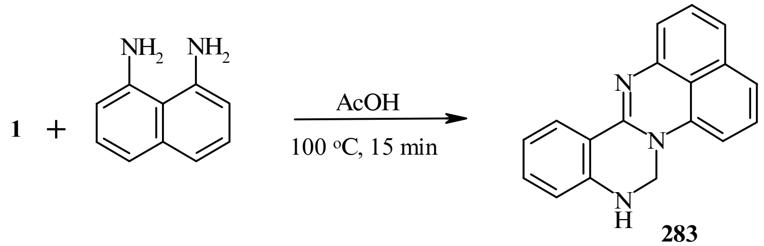
According to the third method, potassium hydroxide and carbon disulfide are added to compound (**276**) (R = H) in alcohol at 0°C, and compound **278** (R = H) is obtained. The latter is converted into the final product **269** (R = H) with a 46% yield by boiling in alcohol (6 h) [180].

The thiadiazoloquinazolone derivative **280** was synthesized by the reaction of the anhydride **281** with the substituted azothiourea **282** [181].



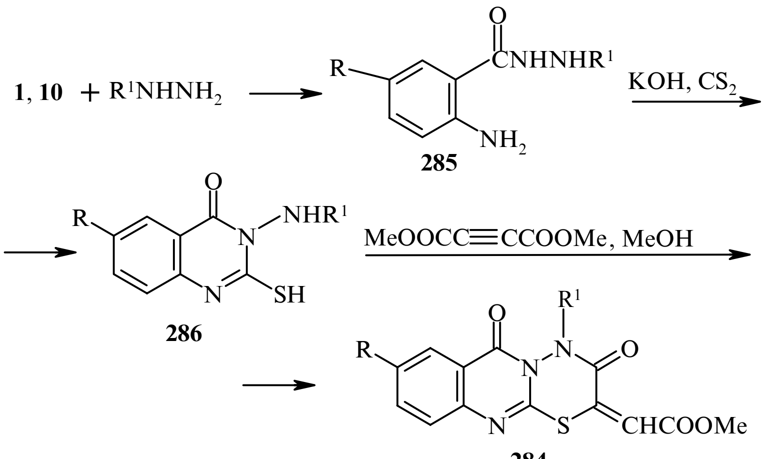
281 **282** **280**

In part 2.2 it was mentioned that the perimidine derivatives **124** are formed with high yields from the anhydrides **1** or **19** and 1,8-diaminonaphthalene. In the case of the anhydride **1** under these conditions the tetracyclic condensed compound **283** was also isolated with a yield of 5% [74].



283

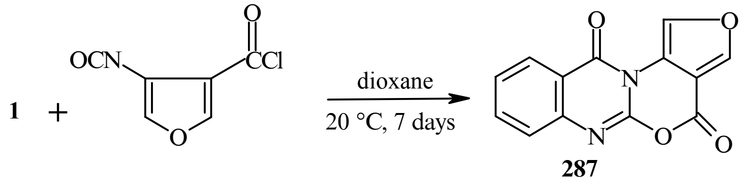
The anhydrides **1** and **10** were converted into derivatives of 1,3,4-thiadiazolo[2,3-*b*]quinazoline **284** in three stages, i.e., reaction with hydrazine or methylhydrazine, cyclization of the obtained hydrazides **285** to compounds **286** (by the action of KOH and CS_2), and reaction of the latter with dimethyl acetylenedicarboxylate [182].



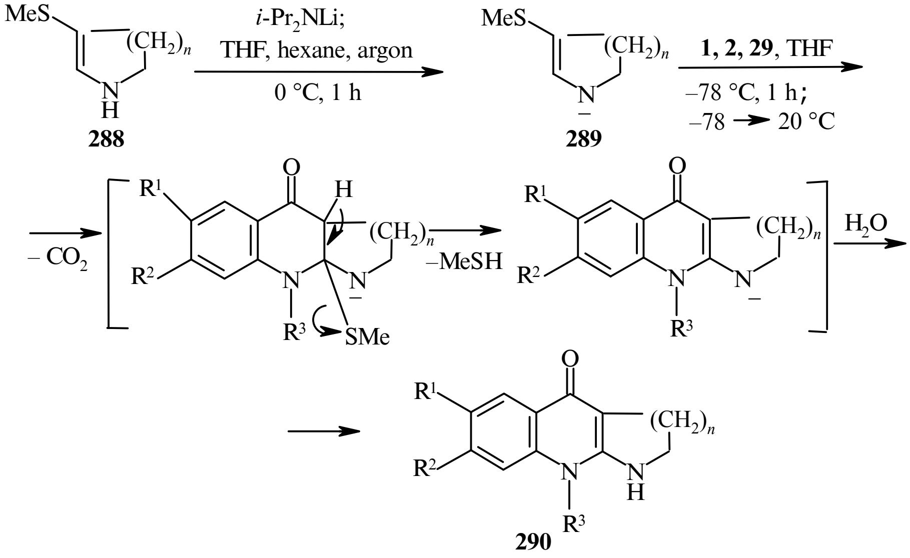
285 **286**

R = H, Cl; R¹ = H, Me **284**

Anhydride **1** reacts with 4-isocyanatofuran-3-carbonyl chloride at normal temperature with the formation of compound **287** [183].

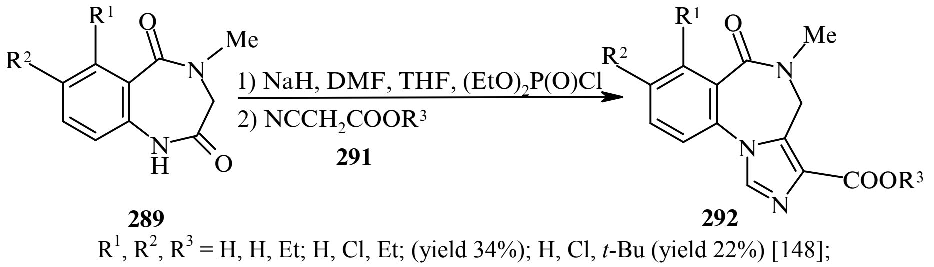


Compounds **288** were converted by treatment with lithium diisopropylamide into the anions **289**, the reactions of which with anhydrides **1**, **2**, **29** gave 9-R^3-4-oxo-3,4-dihydro-1H,4H,9H-pyrrolo[2,3-*b*]quinolines **290** (n = 1) (yields 35-53%), 10-R^3-5-oxo-1,2,3,4-tetrahydro-5H,10H-benzo[*g*]naphthiridines **290** (n = 2) (yields 14-64%), or 11-R_3-6-oxo-2,3,4,5-tetrahydro-1H,6H,11H-azepino[2,3-*b*]quinolines **290** (n = 3) (yields 18-42%). The formation of compounds **290** (n = 1-3) can be represented by the following scheme:



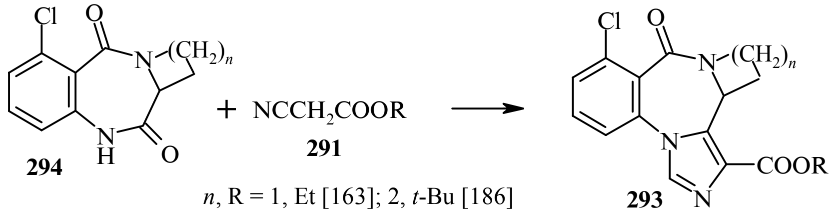
n, R^1, R^2, R^3 = 1, H, H, Me; 1, H, H, $PhCH_2$; 1, Me, H, Me; 2, H, H, Me; 2, H, H, $PhCH_2$;
2, Me, H, Me; 2, H, Cl, Me; 2, H, Cl, $PhCH_2$; 3, H, H, Me; 3, H, H, $PhCH_2$; 3, Me, H, Me;
3, H, Cl, Me; 3, H, Cl, $PhCH_2$

The reaction of the benzodiazepine derivatives **289** [obtained by the condensation of the anhydrides **110** with sarcosine] with cyanoacetic esters **291** in the presence of NaH and $(EtO)_2P(O)Cl$ gave compounds **292** [148, 150, 151, 185].



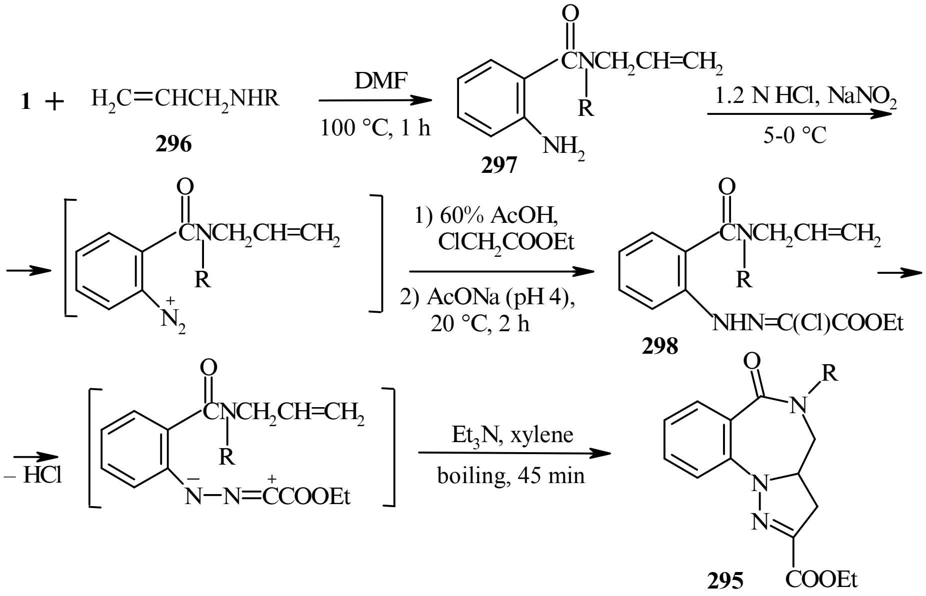
R^1, R^2, R^3 = H, H, Et; H, Cl, Et; (yield 34%); H, Cl, *t*-Bu (yield 22%) [148];
F, H, Et (–) [150]; NO_2, H, Et, (–) [151]; Cl, H, Et, (–) [185]

The synthesis of tetracyclic condensed products **293** (n = 1, 2) also from cyanoacetic esters **291** and benzodiazepine derivatives **294** (obtained by condensation of 5-chloroisatoic anhydride with *L*-azetidine-2-carboxylic acid [163] or with *L*-proline respectively) [186] was claimed in the patents [162, 186].



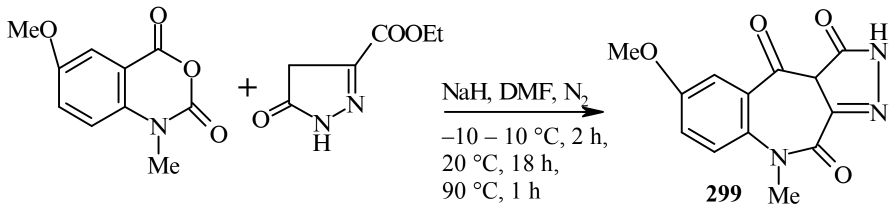
n, R = 1, Et [163]; 2, *t*-Bu [186]

The authors of [187] proposed an original method for the synthesis of derivatives of pyrazolo[1,5-*a*]-1,4-benzodiazepines **295**. Thus, the derivatives of anthranilic acid **297** were synthesized with yields of 47-63 by the reaction of the anhydride **1** with the amines **296**. Compounds **297** were then converted by diazotization and treatment with ethyl chloroacetate into compounds **298** (yields 54-68%). The latter were converted into the required pyrazolobenzodiazepines **295** by cyclization in the presence of triethylamine.

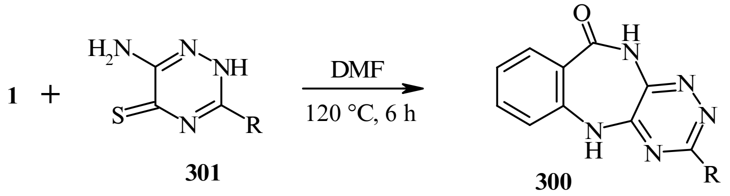


R, (yield of **295,** %): H, (17); Me, (80); $CH_2CH=CH_2$, (75); Ph, (78)

Compound **299** (yield 7.3%) was isolated from the products of the reaction of 1-methyl-6-methoxyisatoic anhydride with 3-ethoxycarbonyl-Δ^2-pyrazolin-5-one in the presence of sodium hydride [89].

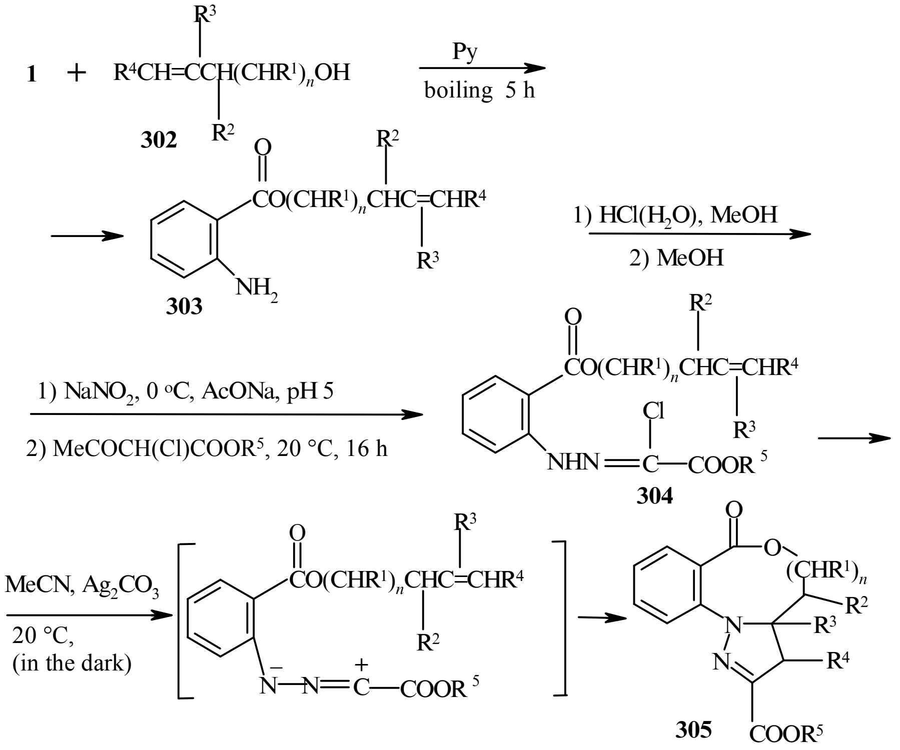


5,11-Dihydro-3-R-10H-1,2,4-triazino[5,6-*b*][1,4]benzodiazepin-10-ones **300** were obtained with yields of 43-64% by heating anhydride **1** with the 1,2,4-triazine derivatives **301** [188].



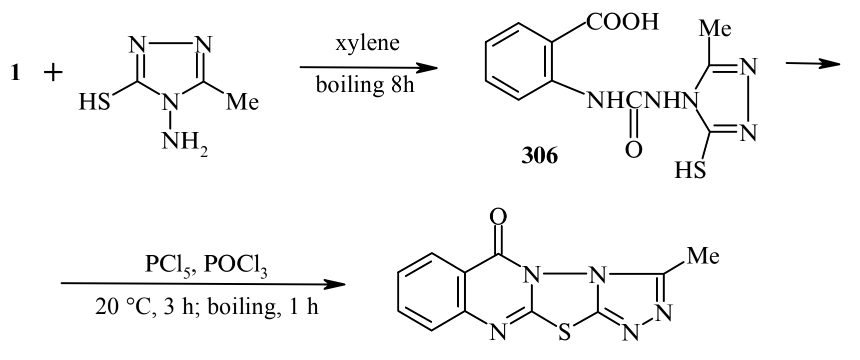
R = Me, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$, cyclohexyl

In the presence of sodium hydride in boiling pyridine the anhydride (**1**) reacts with the alcohols **302** with the formation of anthranilic esters **303** with yields of 41-56%. After diazotization and reaction with α-chloroacetoacetic esters the products are converted into the hydrazonyl chlorides **304** (yields 75-78%). Treatment of the latter with silver carbonate in acetonitrile leads to the tricyclic compounds **305** (yields 14-61%) [189].



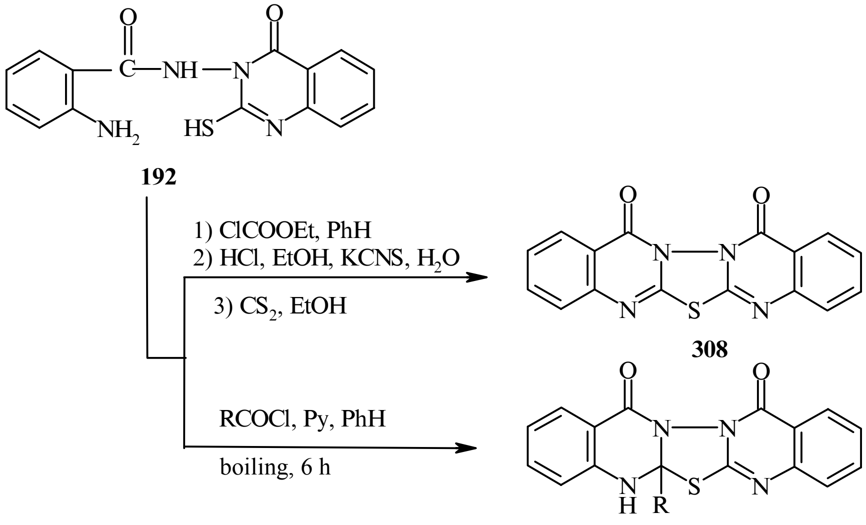
n, R^1, R^2, R^3, R^4, R^5, time, h: 0, –, H, H, H, Et, 72; 0, –, H, Me, H, Me, 15; 0, –, H, H, Me, Et, 24; 0, –, Me, H, H, Et, 24; 0, –, Ph, H, H, Me, 28; 1, H, H, H, H, Me, 28; 1, H, H, Me, H, Me, 16; 1, H, H, H, Me, Me, 170; 1, H, Me, H, H, Me, 63; 1, Me, H, H, H, Me, 20

According to data in [190], the reaction of the anhydride **1** with 1-amino-2-mercapto-5-methyl-1,3,4-triazole takes place in an unusual manner; it leads to the formation not of the corresponding anthranilamide but to the N-substituted anthranilic acid **306** (yield 62%), which is transformed into compound **307** with a yield of 57% when treated with phosphorus pentachloride or phosphorus oxychloride.



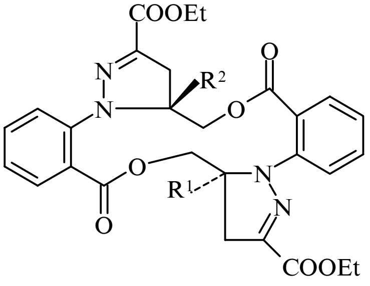
307

The pentacyclic products **308** and **309** were synthesized on the basis of the compound **192** already mentioned in part 2.2 [115]. The authors of this paper proposed three versions for the transformation of the amide **192** into compound **308**: 1) Boiling the amide with chloroformic ester in benzene (yield 55%); 2) treatment of the amide with hydrochloric acid in ether followed by addition of alcohol and KCNS in water (yield 60%); 3) boiling the amide with carbon disulfide in alcohol (yield 51%). Each method takes 8 h. Compounds **309** were obtained by boiling the amide **192** with acetyl or benzoyl chloride in benzene and pyridine for 6 h (with R = Me yield 76%, with R = Ph yield 68%) [115].



R = Me, Ph **309**

When the reaction of the hydrazones **304** was carried out in dioxane instead of acetonitrile the macrocyclic compounds **310-313** were obtained instead of compounds **305** [189].



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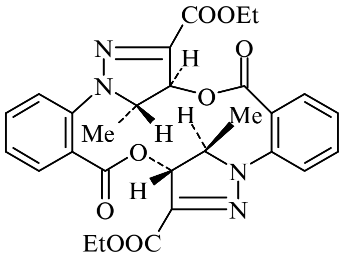

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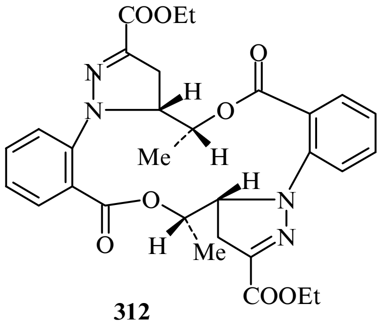

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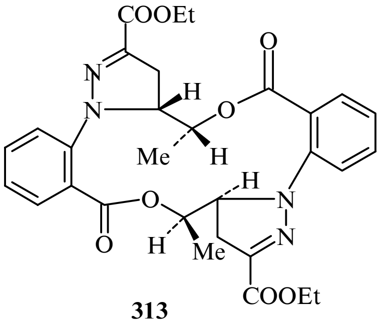

313

Product, time in days (yield, %): **310** ($R^1 = R^2 = H$), 12 (14);

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